THE EFFECT OF TEMPERATURE FLUCTUATIONS ON CLOTRIMAZOLE CREAM BASES

The Effect of Temperature Fluctuation In The Tropics On The Viscoelastic Properties of Clotrimazole (an antifungal) Cream Bases

A THESIS

Presented By

MUSA ABUBAKAR

In Partial Fulfilment for the *Degree* of
Master of Science (Pharmacy) of the
Ahmadu Bello University, Zaria

Department of Pharmaceutics & Pharmaceutical Microbiology
Faculty of Pharmaceutical Sciences
Ahmadu Bello University, Zaria

March, 1983

ABSTRACT

The physicochemical factors affecting semi-solids and in particular emulsified creams have been reviewed. Temperature, humidity, pH changes, Oxidation-rednction processes and microbial contamination are such factors that generally affect the stability of Pharmaceutical and Cosmetic creams.

The flow properties and types of flow of various *types* of pharmaceutical fluids and semi-solids have also been outlined.

An investigation on the macroscopical and rheological properties such as apparent plastic viscosity, yield stress and thixotropy using Ferrenti-Shirley cone and plate viscometry was carried out on various cream bases at different temperatures. Cetostearyl alcohol/Cetyltrimethyl Ommonium oromide were used as mixed emulsifier. The effects of alcohol/surfactant ratio and the total mixed emulsifier concentrations on the visco-elastic properties have also been investigated,

The results of these investigations indicated that temperature fluctuations common to tropical climates affect the physical stability of the creams drastically. It was found that the consistency usually increases with rise in temperature to a

maximum of around 20° - 27° and decreases with further increase therefrom. An exact temperature of maximum stability of 20° was also found to be the same for the commercial sample "Canesten Cream" in the comparative studies conducted in this work,

(in)

ACKNOWLEDGEMENTS

Firstly, I am grateful to Almighty God for giving me the courage and wisdom to undertake this work to a successful end.

I wish to express my profound gratitude to Dr. D. K. Agrawal, Head of the Department of Pharmaceutics and Pharmaceutical Microbiology, for recommending the topic and my sincere thanks go to Dr. J. Y. Gbefwi, for his invaluable help, advice, guidance, constructive critisism and inspiration, which were given to me whenever needed.

I am also grateful to all members of the academic and technical staff of the Department, particularly Dr. (Mrs) G. Prokopczyk, for their support and friendliness and to my colleagues and friends for useful discussions.

Finally, my thanks go to the Ministry of Health, Kano State for the financial assistance which has enabled me pursue this investigation.

Abubakar, M.

DEDICATION

To my father, Mallam Abubakar

who at eighty is too old to continue

and

my child, Maimunatu

who at seven is too young to understand.

DECLARATION

This is to certify that the work reported in this thesis was carried out by me under the supervision of Dr. J. Y. Gbefwi and Dr.(Mrs) Prokopczyk both of the Department of Pharmaceutics and Pharmaceutical Microbiology, Ahmadu Bello University. The work of other investigators is acknowledged and referred to accordingly.

I solemnly declare that no part of this thesis has been submitted elsewhere for a degree.

Musa Abubakar, B.Sc.(Pharm) MPSN,
Dept. of Pharmaceutics and
Pharmaceutical Microbiology,
Faculty of Pharm. Sciences,
Ahmadu Bello University, Zaria.

THESIS APPROVAL

This thesis by Musa Abubakar meets the regulations governing the degree of Master of Science (Pharmacy) of the Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, and is approved for its contribution to science and literary presentation.

Internal Examiners: (1) Dr. J.Y. Obefwi (B.Sc.(Pharm) Hons; M.I.(Pharm.) M; Ph.D.)
*Dept. of Pharmaceutics and Pharmaceutical Microbiology, Ahmadu Bello University, Zaria.

(2) Dr.(Mrs) G. Prokopczyk,(M.Sc; Ph.D.)
Dept. of Pharmaceutics and Pharmaceutical Microbiology, Ahmadu Bello University, Zaria.

External Examiner: Dr. R. N. Nasipuri, (B.Pharm; M.Pharm; Ph.D.)
The Head, Pharmaceutics Dept. University of Ife, Ile-Ife.

*Present Address - Department of Pharmacy, Jos University Teaching Hospital, Jos.

CONTENTS

		Pages
	-	i
Title	-	ii
Abstract	-	iv
Acknowledgement	-	v
Dedication	-	vi
Declaration	-	vii
Thesis Approval		
CHAPTER 1		
1. Introduction - General	-	1
2. The Stability Factors of Pharmaceutical Creams		2
3. Temperature and Humidity effects on Semi-solids		6
4. Rheological Tests and Physical Stability of Emulsions		16
		21
a. Rheological Measurements		24
b. Flow Properties of Fluids		24
i. Newtonian Flow		26
ii. Pseudoplastic and Dilatant Flow		31
iii. Bingham or Plastic Flow		32
iv. The Yield Stress (value)		34
v. Thixotropy		42
5. The aim of the work		
CHAPTER 2		
Materials and Methods of Investigations		44
1. Materials		

		Pages
2.	Solubility Determination	48
3.	Ferrenti-Shirley Viscometer	55
4.	Method of Preparation of Cream bases and Storage	71
	CHAPTER 3	
	Results	
1.	Macroscopical	78
2.	Continuous Shear Rheometry	80
	CHAPTER 4	
	Discussions and Conclussions	
1.	Continuous Shear Rheometry and Low Temperature	95
2.	Shear Stress	98
3.	The Yield Stress (value)	100
4.	The Apparent Plastic Viscosity	102
5.	Thixotropy	103
6.	Formulation Considerations	105
7.	The 'Self-bodying Action' of mixed emulsifier and Gel-network formation	107
8.	The Effect of Concentration of mixed emulsifier concentration	114
9.	The Effect of Surfactant Alcohol Ratio	117
10.	Conclusion	124
	References	128
	Appendixes I - VI	136

CHAPTER ONE

The Effect of Temperature Fluctuations In The Tropics On The Viscoelastic Properties Of Clotrimazole Cream Bases.

INTRODUCTION

1.1 Clotrimazole $C_{12}H_{17}Cl\ N$ Mol Wt 344.8 - Bis-phenyl -(2-chloro-phenyl)-1- Imidazolyl-methane, is a broad spectrum antimycotic with fungicidal activity extensively used in Nigeria as a 1% w/w water miscible cream (Canesten Bayer).

The term "cream" in pharmacy and medicine is applied to viscous emulsions of semi-solid consistency intended for application to the skin or mucous membrane. Griffin (1954) defined a cream emulsion as one which exhibits certain degree of body or apparent viscosity sufficient to form a heavy fluid or a soft easily deformed gel. It may be an oil in water (o/w) or a water in oil (o/w). In pharmacy and cosmetic industries, creams are referred to o/w type. Emulsification is the most common and most useful method of applying a medicinal and cosmetics agent to the skin. Among other things emulsification promotes acceptability and cosmetic elegance, Jellinels (1970). Emulsions are easy to apply and spread

on skin and hair, are economical because they often contain much water, yet after having been rubbed on, leave adequate concentration of active substances on the skin and they make possible the simultaneous use of oil-soluble substances in the same preparation. Emulsion usually break down after being applied to the skin and the emulsifying agent then becomes active as a wetting agent, thus, facilitating the penetration of other active components. Emulsification also allows almost any consistency to be achieved i.e from fluid (lotion) emulsions to quasi-solid ones which are more likely to retain stability inspite of temperature fluctuations than anhydrous creams. The appearance and consistency of emulsified product is generally very satisfactory. They avoid the sticky, greasy feeling that anhydrous products often leave on the skin and the insubstantial thin sensation of pure aqueous products.

Such formulations are thus very important and their technology essential. Rheological measurements are valuable for reasons of controlling consistency and quality of raw materials and final products and the processes used in manufacturing and packaging and filling. Rheological investigations are also used to investigate the capacity of formulations to suspend solids or

immicible liquids, monitor the affects of formulation changes; storage time and the temperature changes. Ultimately the investigations can indicate how the product may be assessed with regards to its usage i.e. spreading or adherence to the skin and bioavailability of the medicament with subsequent absorption into the body. Usually investigations are performed to permit formulation of a current formula, quality control or duplication of a competative product. It is therefore obvious that the characterisation of various pharmaceuticals of this consistency using their rheological products is very important in pharmacy.

1.2 The Stability Factors of Pharmaceutical Creams.

Lintner (1973) and Enever (1977) defined stability as the capability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specification. Stability is also defined as the time from the date of manufacture of the formulation until its chemical or biological activity is not less than a predetermined level of labelled potency and its physical characteristics has not changed appreciably or deleteriously.

The stability of many pharmaceutical products is often affected by many factors singly or in combinations. Factors such as isomerization of certain compounds, decarboxylation, pH change, radiation, humidity and temperature fluctuations cause decomposition of the product through oxidation, reduction or hydrolysis. Other factors include incompatibilities (physical, chemical or therapeutic) which may lead to either potentiation of the therapeutic effects of the ingredients, destruction of the effectiveness of one or more of the ingredients, or occurance of a toxic manifestation within the patient or consumer.

Many factors attribute to the stability of emulsified systems: the particle size, particle size distribution, the difference in density of the two phases, the viscosity of the continueous phase and of the completed emulsion. The sedimentation or creaming rate is inversely proportional to the viscosity of the medium as given in the Stokes equation:

$$V = \frac{d^2 (P - P_o)g}{18\eta_o} \quad \ldots\ldots (1)$$

where V, is the rate of sedimentation or creaming, d, is the mean diameter of the dispersed globules or particles, P and P_o are the densities of the dispersed phase and continueous phase respectively; η_o is the viscosity of the medium and the g, is the acceleration due to gravity. The effectiveness and amount of emulsifier used, and the condition of storage including high and low temperatures, agitation during storage or use also attribute to stability factors. Considering cosmetic emulsion in which lack of creaming is required for good stability, small particle size may be said to promote stability, Schwartz and Perry (1949).

The stability of emulsion is affected by almost all factors involved in formulation and preparation. In formulations containing sizeable amount of emulsifier, stability is predominantly a function of the type of concentration of emulsifier, Griffin (1974) and Becher (1965). Neither creaming nor sedimentation is however fully a creteria for physical stability in the sence, but the growth of the oil particles by coalescence which leads to separation of such systems is more important. The increase in free coalescenced oil globules which occur with

time is expected since the emulsified state is thermodynamically unstable and, at least, represent a pseudo equilibrium state.

1.3 Temperature and Humidity Effects on Semi-Solids.

The effects of humidity and temperature fluctuations on the stability of semi-solids systems generally is a serious problem in the tropics like Nigeria where there is a great variation in temperature between the times of the day and the periods of the year even within the same locality and an even greater variation at different places and periods of the year.

Table I - from metrological observation - (1980) gives the variation of air temperature and relative humidity in Samaru, Zaria. From the table, it can be seen that within a year, a mean maximum temperatures of up to 31.5^{o} can be obtained while the mean minimum is about 17.8^{o} i.e. about 13.7^{o} variation within the year which can be very serious in the rheology of emulsions. It can also be seen that these are only the means in the year, the temperature does get as low as 11.7^{o} around December and as high as 36.5^{o} around the month of April. In another data, Synge (1975) Figure 1, gives a rough climatic

zones of the whole Nigeria which shows that the minimal temperature can get as low as 4^{o} at night and as high as 40^{o} during the day in the extreme northern part of the country, like Sokoto and Maiduguri. Down in the southern parts of the country however, near the sea coast, the range of temperatures is narrow; about 21 - 35^{o}.

The average relative humidity ran parallel with the temperature and an annual mean of about 38.7-49.8% at Samaru, Zaria, is recorded and unevenly distributed throughout the year as can be seen from table I, while it is about 60 - 70% average down the southern part of the country and is more evenly distributed throughout the year as can be seen from the foot note of figure I - 1.

The effects of temperature fluctuation on semi-solid emulsified systems can be appreciated due to the fact that these systems are inherently thermodynamically unstable. Garret (1965), Kitcherner and Masselwhile (1968), and Guiseley (1970, 1971) all showed that the result of the positive surface energy of the particles or globules in emulsified systems was responsible for the instability mainly because these particles or globules which are in a divided state strive to come together so as to reduce their surface energy,

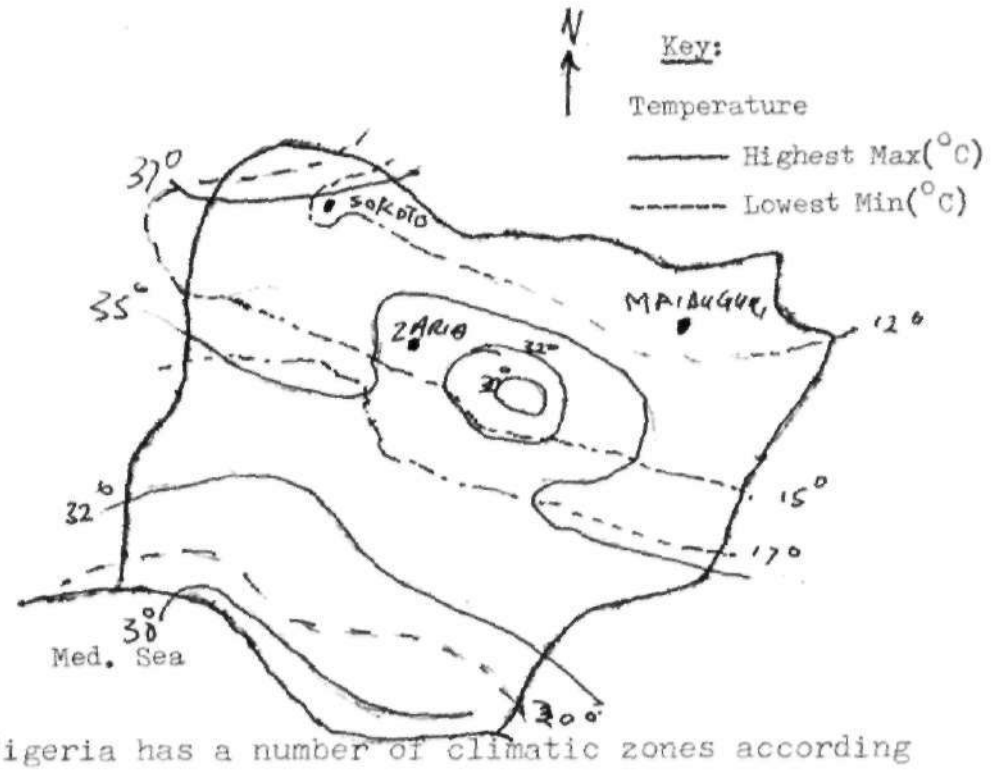
Table 1 - Relative Humidity and Air Temperature of Samaru

(Metrological Observations Centre, Institute for Agricultural Research, A.B.U., Samaru, Zaria 1980)

	RELATIVE HUMIDITY					AIR TEMPERATURE °C				
Month	1980		1954-1980					1938 - 1980		
	A.M.	P.M.	A.M.	P.M.	Min.	Max.	Mean	Min.	Max.	Mean
JANUARY	16.3	15.1	17.7	13.9	13.2	31.2	22.2	13.9	30.3	22.1
FEBRUARY	13.4	14.0	15.2	10.8	15.8	32.4	24.1	16.0	32.7	24.4
MARCH	21.2	12.8	25.6	14.2	18.8	35.4	27.1	19.5	35.8	27.4
APRIL	37.4	23.4	47.9	29.0	21.9	36.5	29.2	21.7	35.7	28.7
MAY	68.4	51.4	63.6	43.4	21.3	33.0	27.2	21.2	32.9	27.4
JUNE	74.9	63.6	72.6	57.3	19.8	30.3	25.1	19.9	30.7	25.4
JULY	81.3	68.8	79.5	66.2	19.2	28.7	24.2	19.2	28.4	23.9
AUGUST	93.1	71.7	81.7	69.7	19.4	28.1	23.8	19.3	27.7	23.5
SEPTEMBER	75.5	62.6	75.9	62.9	19.4	30.6	25.0	19.1	29.3	24.2
OCTOBER	66.0	43.9	60.6	43.1	18.8	32.0	25.4	17.7	31.4	24.8
NOVEMBER	28.2	19.5	29.2	21.4	13.9	31.9	22.9	15.4	31.6	23.5
DECEMBER	21.3	17.4	21.1	16.4	11.7	28.4	20.1	13.8	30.3	22.1
TOTAL MEAN	49.9	38.7	49.2	37.4	17.8	31.5	24.7	18.0	31.4	24.8

Note: Before 1953 observations taken at 0.800 and 1300 G.M.T.
After 1953 observations taken at 0900 and 1500 G.M.T.

Fig. I.1 The Climate of Nigeria



Nigeria has a number of climatic zones according to altitude and distance from the sea, but generally speaking there are two well-marked seasons - a dry and a rainy one. The dry season extends from November to April in the North, and to a shorter period (December - March) in the South. At this time the north-easternly dust-laden Harmattan wind blows from Sahara, causing the temperatures in the North to vary considerably from 4° at night to 40° during the day.

Source: (Nigeria - The land and its people by Richard Synge. Macdonald and Company (Publishers) Limited, 1975, Page 54).

the colliding particles are therefore observed to fluctuate, coalesce or fuse. The rate of corsening of an emulsion therefore depends upon the effectiveness of inter-facial barrier to coalescence and upon the frequency and duration of globules encounter, Prince (1967) and Garett (1965). High temperature causes increased thermal agitation and decreases the viscosity of the continueous phase because it increases the frequency of collision of the dispersed phase particle/globules and accelerate the tendency for the emulsion to crack. On the other hand, there may be certain instances where low temperature can promote instability as in the rate of polymerization of formaldehyde at temperature below 15^{o} and in certain oxidation processes where oxygen content of the solution is a critical factor in the reaction. Low temperature can also have an adverse effect on stability on emulsion creams and ointments. The stability of most emulsions is said to diminish at near or below 0^{o}, Pickett (1977), due partly to altration of the emulgent properties or formation of ice crystals which rupture the interfacial film. But, fortunately the effects of low temperatures are generally of no significance compared with the adverse effects of higher temperatures in the tropics.

Considering the processes usually undergone in the production and use of emulsified products, the effects of temperature fluctuation can hardly be effectively controlled. The effects begin from the time the product is being made to the time the consumer finally applies it to the affected part of the body. For instant, in the making of cream emulsion or ointment, the height of temperature reached and the length of time that temperature is maintained makes a great difference in the ultimate stability of the same formulation, Boylan (1966), Davis (1969), Barry and Eccleston (1973) and Barry (1975). The method and rate of cooling when the product has been finally mixed are also equally as important variables, Boylan et. al. (1962), Griffin (1975) and Barry (1975). There are some instances too, particularly in the manufacture of cosmetic creams where the ingredients will fail to emulsify properly if they are processed at too high temperatures (and certainly at low temperatures, they do not emulsify at all). Ekman and Sjoholm (1978) have postulated that the increased thermal energy leads to leakage of the entrapped dispersed phase of an emulsion into the dispersion medium.

Simon et. al (1961) and Boylan et. al (1962), while ingestigating the temperature induced rheological changes of an oil in water emulsified systems containing an 8% w/w white wax and 25% oil, found that emulsions prepared at 80° or less and cooled slowly after preparation were least thixotropic initially. These products had the most consistent viscosity on aging. Emulsions prepared at the same temperature and cooled rapidly as recommended by Barry and Eccleston (1973), Talman and Rowan (1970 a,b) and by B.P. and B.P.C. (1973) were found by microscopic observation to contain smaller dispersed globules but were highly aggregated, which probably accounted for the initial greater degree of thioxotropy, rheological instability and rapid separation. Barry and Shotton (1967 a & b), Barry and Saunders (1968, 1972 a & b) Davis et al (1968), Davis (1969), Talman and Rowan (1970) and Bourret and Bardet (1981) all reported a decrease in the rheological properties of all fluids and visco-elastic materials upon increase in temperature. Osborn and Lee (1951) reported a drastic decrease of apparent viscosity of 35%w/v acacia mucilage of 2.0 Poise at 26° to 0.63 Poise at 63°. Davis and Rawson (1957) reported a decrease from 7.00 Poise at 20° to less than 2.00 Poise at 60° for a 2% medium viscosity grade

sodium carboxymethylcellulose. This dependence of viscosity on temperature may be small and due only partly to the effect of temperature on suspending medium or greatly as due to increase or decrease interaction between particles. The variation of viscosity with temperature is often described by Arrhenius equation(1887) for chemical reaction. The equation which involves the activation energies at constant shear rate or shear stress, as the case may be, William (1958), Miller (1963) and Lenk (1978).

$$\eta = B\, e^{E/RT} \quad \ldots\ldots (2)$$

where B - is a constant depending on molecular weight and volume, time, pressure and concentration.

E - is Apparent Activation Energy of viscous flow (to initiate flow between molecules).

R - is the universal gas constant.

T - is the Temperature.

Generally, an increase in temperature causes a break down in the structure responsible for the viscoelastic properties and the model representation becomes simpler (Voight-Kelvin models of Barry (1975)). Barry and Shotton (1968) and

Carless (1977) have predicted a rough guide for many liquids that the viscosity decreases by about 2% for each degree rise in temperature.

As pointed out, Arrhenius equation cannot apply to emulsion to any degree of certainty in view of its complex nature. Arrhenius equation can only be valid when the break down is a thermal phenomena with an activation energy of about 10 - 100 kcal/mol and when the reaction remains the same and therefore not related to emulsions where the thermal reaction could vary significantly with different type of formulation, Lenk (1978), Sherman (1963, 1964) and Eirich (1956 and 1960).

Ben-Kerrour et al (1980) has studied the effect of temperature and emulgent concentration dependence of pseudoplastic materials rheologi-callyand pointed out that it is true that elevated temperatures are not very appropriate for product containing suspending or emulsifying agents such as methylcellulose which coagulate on heating and proteins which may be denatured. Temperature changes influence the partitioning of emulsifier between phases, the crystallisation and melting of certain lipids, the chemical decomposition and the rheological behaviour.

The rate of heating and cooling will be particularly significant in determining the crystalline nature of any waxes that are present which in turn determine emulsion stability. The effect of temperature though may not be the same for each emulsion, so that comparism must be made with great care.

Humidity or moisture content in air if unprotected may cause deterioration of emusified products, creams or ointments e.g. glycerin suppositories can absorb moisture and become opage. Stability of semi-solids and emulsions is affected mainly through hydrolysis. The effect will depend upon the humidity and temperature of the atmosphere and the pH of the medium. The presence of moisture may in some instances also increase the rate of oxidation of susceptible products like oils and fats in emulsions since oxygen is dissolved in the water layer surrounding the drug particle, Gore and Ashwin (1967), Picket (1978) and Ostwald (1910 a & b) also indicated that generally water sorption of creams reduces their consistencies and if too much, it can bring about separation of the phases. On the other hand water lost through evaporation can equally be important in oil-in-water emulsions and may cause cracking of these systems all together or at least phase inversion

and other degradation processes such as bleeding and surface oxidation of oily parts particularly on aging, King and Mukherjee (1939) and Sprow's and Beal (1966). For dermatological creams and cosmetics, fortunately, control of moisture sorption or evaporation can be effectively controlled by the addition of humactants such as glycerin and/or keeping the product in a well closed container which in addition gives mechanical protection.

1.4 Rheological Tests and Physical Stability of Emulsions:

There are various methods for determination of stability of emulsion but the rheological ones are the most feasible. They are the most popular and have convenient approach used to evaluate emulsion. This entails the measurements of consistency, viscosity, yield stresses (conventional and static) thixotropy or other rheological behaviours. Such measurements have been used to ensure some controls and to follow changes associated with emulsion instability. Control is possible because emulsion viscosity is dependent on globules particle size of the dispersed phase, the nature of the emulsifier and its concentration, phase volume ratio and the viscosity of the external phase all

of which are important in determining emulsions behaviour. The dispersed phase globules size-frequency analysis of an emulsion from time to time as the product ages was claimed to be the only precise method of determining emulsion stability by King and Mukherjee (1939), Sherman (1964, 1968), Becher (1965) and Hamil and Petersen (1966). For rapidly breaking emulsions, macroscopical observations of the separated internal phase is adequate. In microscopical method, the diameter of the globules or particles are measured and a size-frequency distribution of the particles ranging say from 0.01 - 0.9 μ, 1 - 1.9 μ etc is made and a plot of particle size versus the frequency or number of globules in each size range drawn. Such investigations have been reported by Finkle, Draper and Hilde Brand (1923), Rowe (1965) and Rehtold (1967). Other authors however, do not share the same views totally. Cooper (1937) reviewed the particle size-frequency method and pointed that the specific surface area distr bution was more acceptable as a creteria for stability than was the size distribution. It must also be remembered that stability is not strictly related

to initial particle size or particle size frequency distribution. Probably a method which considers coalescence of the dispersed globules of an aging emulsion or separation of the internal phase of the emulsion over a period of time may be more meaningful. Vander Tempel (1953), Laurence and Mills (1954) and Sherman (1964) all worked extensively on the stability of emulsions on aging and correlated their dependence on the kinetics of globules' coagulation. Tingstad (1964), also reviewed the physical stability testing of pharmaceuticals generally in which he described that the stability of most emulsions depend mainly on the length (or strength) of the interfacial film surrounding the dispersed particles. If this assumption is correct, therefore the rate of coalescence of the internal phase is a more valid measure of emulsion stability. Reddy and Foglar (1981) included turbidity analysis as a test of stability.

Probably the most important consideration with respect to pharmaceutical and cosmetic emulsion creams is the physical stability of the internal phase as discussed above and maintenance of elegance with respect to appearance, odour and

and colour, in totality, the rheological characteristics. Just as the flavour, odour and appearance of food affects a person's psychological response to food so does the appearance and rheology of most fluids and semi-solid emulsions and cosmetic products affect the user's psychological response towards that product, hence the subject of psycho-rheology of Herper (1953) and Martin et al (1964). These properties must be met besides the facts that the products must possess the correct physico-chemical and biopharmaceutical properties. The correct consistency of such products help to ensure that a suitable dose is applied to the skin. Barry and Grace (1972) and Barry and Meyer (1973). This is particularly important with vehicles that incorporate potent drugs such as corticosteroids. The elegance and smoothness of the product have been shown to be directly proportional to the consistency of the base; Chun et al (1958) and Marriot (1961). Since the base forms the major part of the preparation, it is important that the base cream must be stable. The consistency of the base and other rheological parameters have also been shown to be related to the release of the active medicament as well as the bioavailability,

Patton and Robinsion (1975) and Sheriff and Enever (1979); and the ability of the base to take up solid or fluid medicament. The consistency of a cream may also affect the rate of absorption of the medicament by the skin and their flow properties. Skauren et al (1949) reported that the consistency of semi-solid vehicles may influence the release of drugs which they contain. A greater release of the active medicament is generally possible from the softer, less viscous bases. The absorption of the material through the skin has been related to diffusion rate, Higuchi (1960) which is in turn influenced by rheological factors. Consequently therefore, the viscosity of semi-solid products may affect absorption of these topical products through the intermediate effect of viscosity or diffusion.

Barry and co-workers have conducted investigations in the rheological properties of an oil-in-water emulsions using Cetyltrimethyl ammonium Bromide (CTAB) and Cetostearyl alcohol as mixed emulsifiers, Barry and Eccleston (1973, 1975). The effect of temperature variations on the consistency of such systems have also been

investigated by Davis *et al* (1969), Bourret and Bardet (1981) and Jonsson and Wennerstron (1981). Rheological parameters have been shown to vary with the mixed emulgent concentration, Talman *et al* (1967 a, b). Rheological stability of emulsions was also shown to be affected by the surfactant / alcohol ratio using continuous shear viscometry, Van Wazer (1963), Davis (1969) and Lenk (1978).

(a) Rheological Measurements

The manufacturer of medical or cosmetic creams must be capable of producing a product with an acceptable consistency and must be able to reproduce these qualities each time a new batch is prepared. The rheology of an emulsion ranges from mixing and flow of materials, their packaging into containers and their removal prior to use whether by pouring from bottles, extrusion from tube or passage through needle. The consistency can thus be varied. Very dilute dispersion emulsions may exhibit Newtonian flow whereas those with considerable amount of 'solid' in the continuous phase, or which are frozen, may function essentially as solids. In between these limits lies most of the semi-solids or quasi-solid

emulsions which makes quantitative comparism between different formulations complicated because they combine both liquid and solid properties or are viscoelastic, Kosten Bander and Martin, (1954), Sherman (1963 b, 1964, 1970), Martin et al (1964) and Lenk (1978). For viscoelastic materials creep testing and creep relaxation measurements are applied. These parameters are readily obtained by instanteneously loading the sample and measuring the resultant deformation as a function of time and then the recovery after the sample is unloaded. A viscometer that measures the creep and creep relaxation has been described by Barry (1975). A typical creep and creep relaxation curve, of a type obtained for many viscoelastic emulsions is illustrated in figure 1 .2 using a concentric cylinder creep viscometer, Barry (1971). The shape and size of the creep compliance and relaxation is fundamentally important in viscoelastic measurements and other parameters may be related back to it. The test starts with the material in its rheological ground state i.e. the material possesses no internal stresses or strains. The measurement again simply flexes the organised structures such as floccules or gel network but does not disrupt them. This is referred to as non-destructive rheological test.

Other rheological measurements employed by other workers using soft paraffin o/w cream is the continuous shear experiments - Talman et al (1967), Davis (1969) and Barry and Grace (1971). In continuous shear method, which is destructive and therefore does not measure the rheological parameters of the emulsion in their ground state; flow characteristics involves the measurement of shear stress at various arbitarary value of shear rate (or vice-versa) within the region of laminar flow using a cone and plate viscometer like the Ferrenti-Shirley viscometer which may be available with an automatic program unit, enables continuous rheograms to be plotted at varying sweep times and maximum shear rates. The instrument has been used to study a range of ointment bases by Beylen (1966, 1967), cream bases stabilised by complex film by Talman et al (1967) and soap, water amphiphile/oil mixtures by Barry and Shotton (1967). A typical continuous shear rheogram of typical emulsion is dipitched in figure 1.3. Again the shape and size of the rheogram is of fundamental importance. It can vary with the temperature, sweep time, shear history and the rate and height of shear stress or strain. The advantages of cone-plate viscometer in continuous shear are many such as uniform rate

of shear across sample, small sample size of 1 ml or less, good temperature control, easy to clean and fill and the automatic control allows flow curves to be obtained quickly and under standardized conditions. But it is unsuitable for coarse suspensions or emulsions owing to the narrow gap of cone and plate. Flow properties of many other fluids are given as under -

(a) Flow Properties of Fluids

The viscosity of fluids (gases or liquids) has been defined as the resistance to the movement of molecules; a movement usually described as flow. There are many types of flows. Actually few materials adhere strictly to the theories of the nature of flows.

(i) In Newtonian type of flow, shear stress versus shear rate relation remains constant over a wide range assuming other conditions remain the same. For Non-Newtonian fluids Van Wazer et al (1963) and Lenk (1978), have postulated the following general equation.

$$\eta = F (S, T, t, p, C \ldots\ldots) \text{ --- } 3$$

where η = coefficient of viscosity

S = shear stress, itself a function of shear rate, $\dot{\gamma}$

T = Temperature

t = time

p = pressure, itself a function of volume

C = concentration.

and where the multiple dots includes for example, molecular parameters such as molecular weight, molecular weight distribution, compressional variable e.g. crystallinity, the presence of plasticiers, fillers, stabilisers, impurities etc. and factors relating to the processing history e.g. orientation residual stress etc. For Newtonian fluids, the coefficient of viscosity or simply viscosity , is given by $\eta = \frac{S}{\dot{\gamma}}$, provided that the stream line flow or laminar flow is maintained and is independent of the rate of shear (fig. 1.4A).

For polymers, concentrated heterogeneous dispersions, including colloidal dispersion, other emulsions, suspensions and ointments whose substance exhibit high molecular weight, the viscosity is found to vary by many orders of magnitude with varying rate of shear or shear stresses, Van Wazer (1963), their characteristics consistency flow curves or rheograms could be plastic, pseudoplastic or dilatant (fig. 1.4C). Lenk (1968), pointed out

that all types of rheograms may form part of a general respond pattern (fig. 1.4G).

(ii) Pseudoplastic and Dilatant Flow

A pseudoplastic material (fig. 1.4B), is one whose flow behaviour, when subjected to a shear rate from zero upwards shows a convex curvature with respect to shear rate axis. Thus the shear stress S, does not increase linearly with increase shear rate $\dot{\sigma}$. This can be described by the equation:

$$S = \eta_{NW} \dot{\sigma}^{n} \qquad \text{----- 3(a)}$$

Where η_{NW} = coefficient of Newtonian viscosity.

The exponent, n is less than one for pseudoplastic body. In the dilatant type of material (fig 1.4C), the behaviour is exactly opposite the pseudoplastic with the rheogram[a] concave curvature with respect to shear rate and therefore has the n-exponent in equation 3(a) greater than one, Lenk (1967), Van Wazer et al (1963) and Reiner (1960).

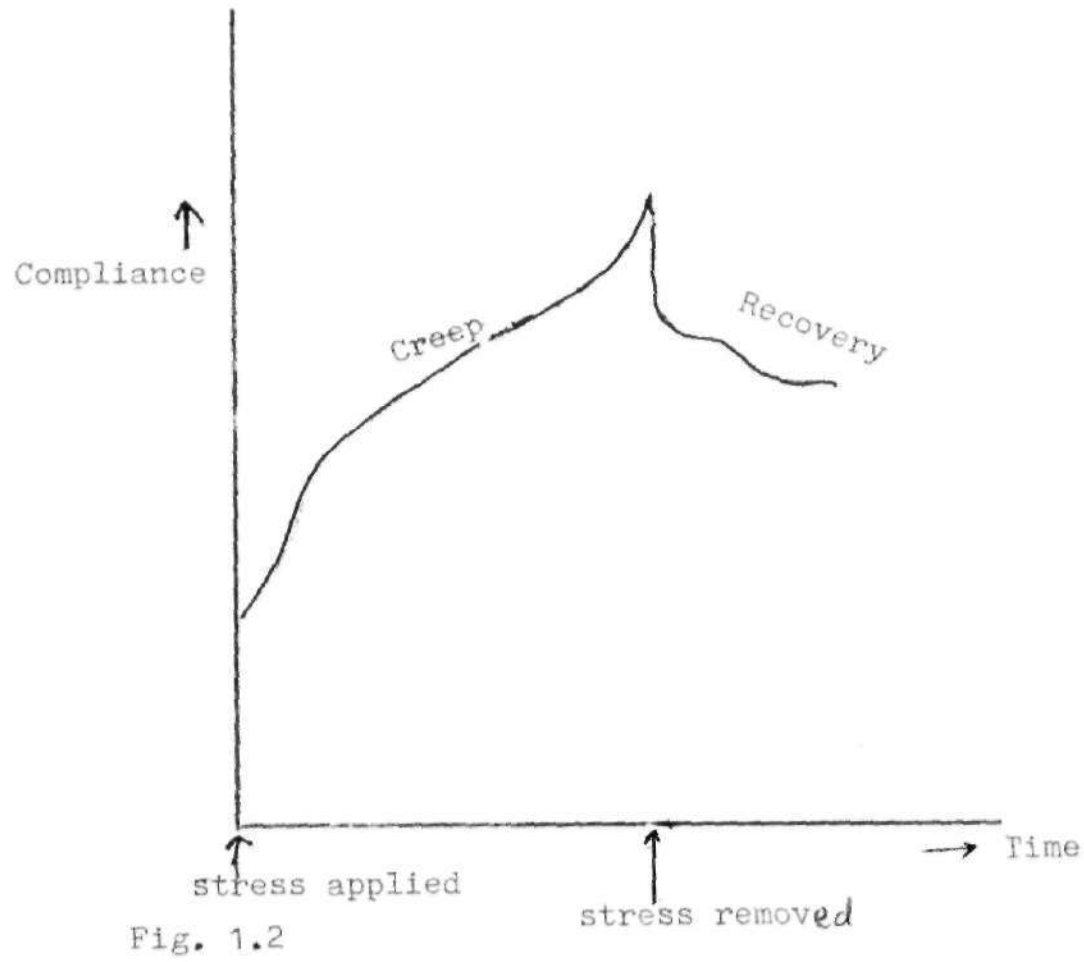


Fig. 1.2

A typical creep compliance and recovery curve for a viscoelastic emulsion (Barry, 1971).

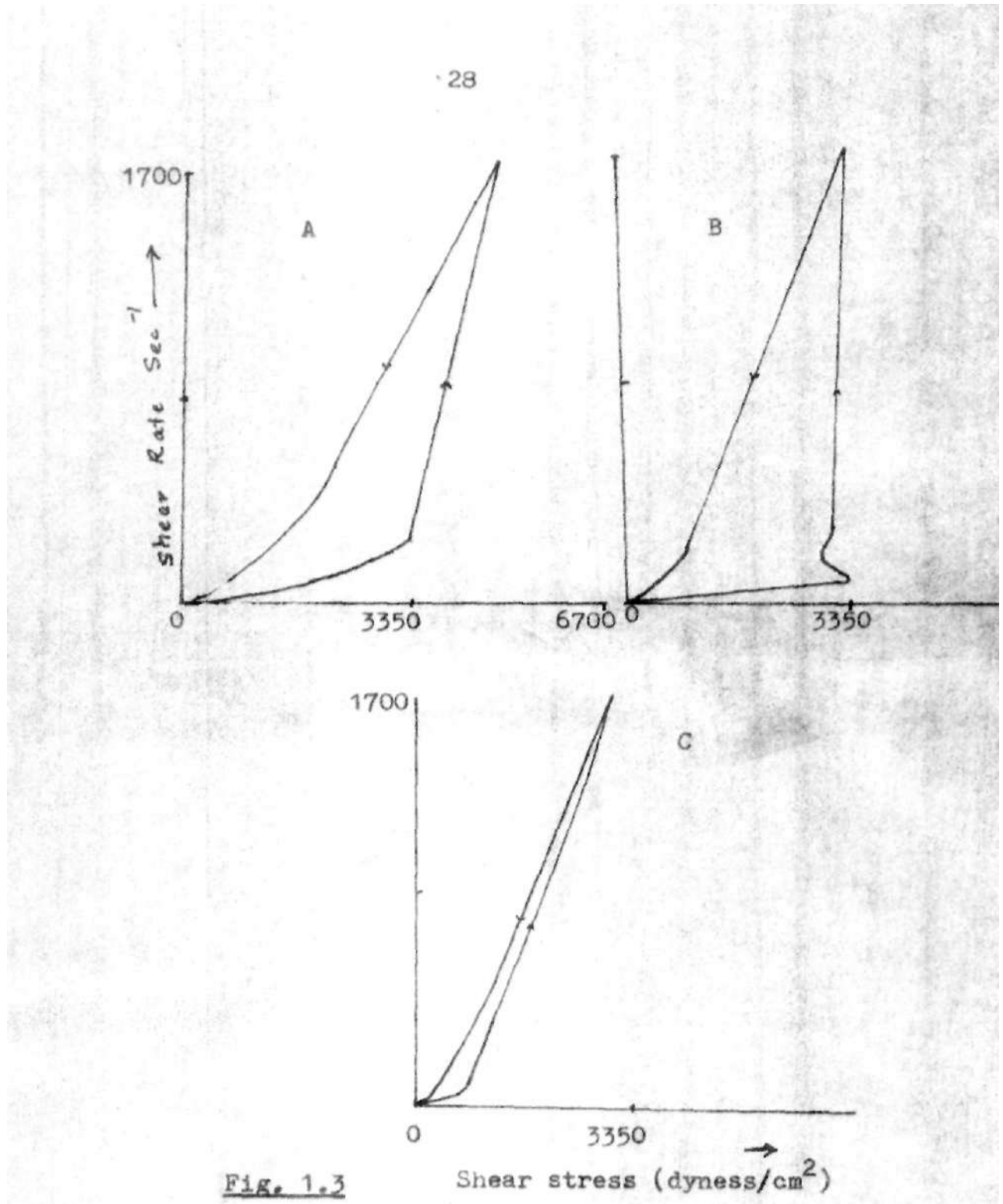
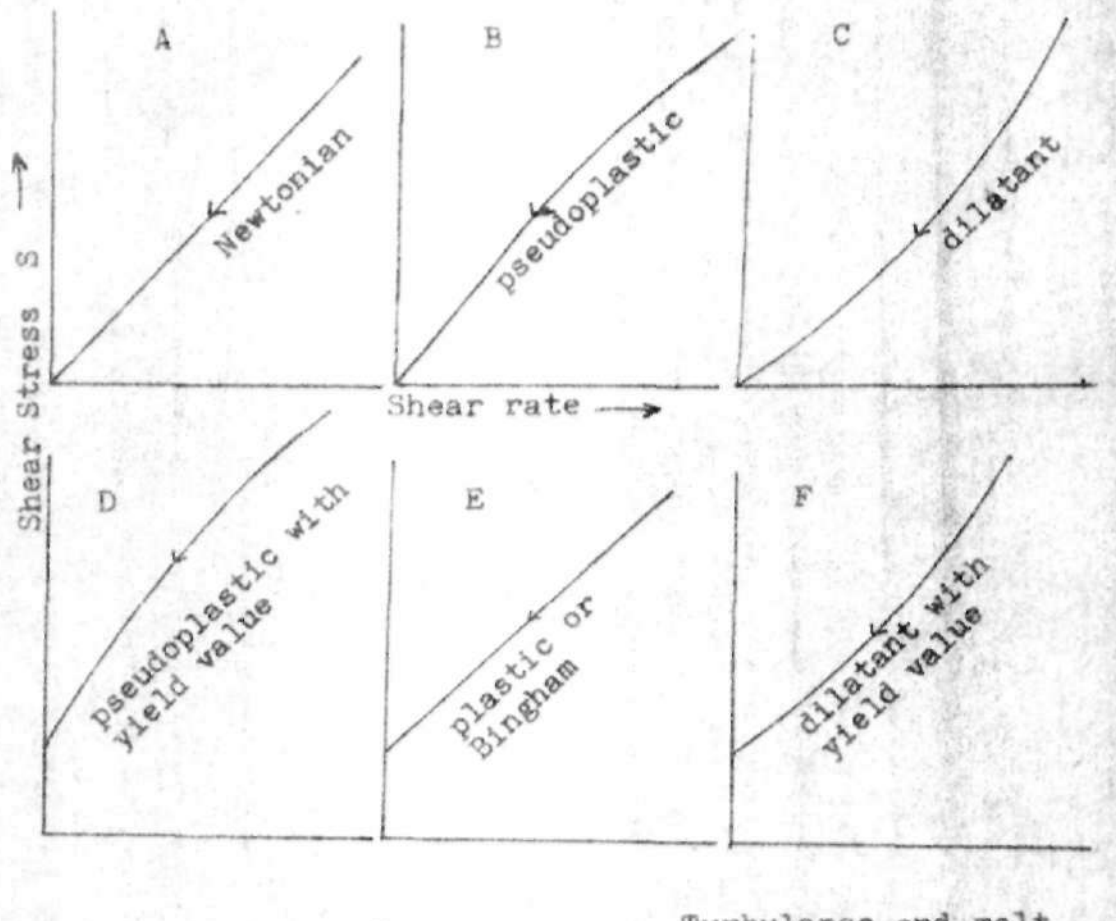


Fig. 1.3

Typical Continuous shear Rheograms for three creams. Temperature 25° Sweep time 240 sec.
A-Aqueous B-Cetrimide C-Chlorhexidine (Davis 1969).



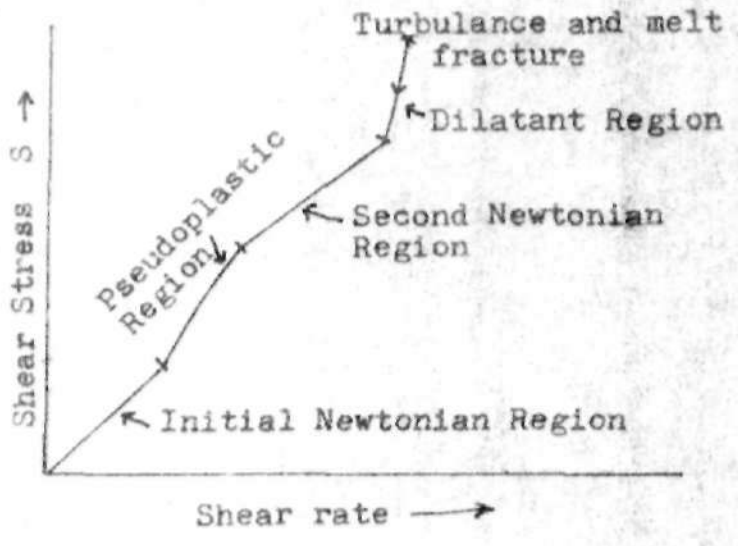


Fig. 1.4

Flow phenotypes A - F of fluids and generalised flow curves of viscoelastic materials, G. (Lenk, 1978)

Solutions of suspending agents such as tragacanth, gelatin, carboxymethylcellulose and other water-soluble mucilages and gum exhibit pseudoplastic type of flow. These materials usually consist of long-chain molecules or other complex structures which are disarranged and matted together at rest and remain so at low shear rates because of decrease in viscosity with increase shear rates. Pseudo-plasticity, is also referred to as "shear rate thinning" effect while the dilatant is termed "shear rate thickening" effect. The latter types of materials include starch made into paste in cold water. This effect is common in deflocculated systems because deflocculated particles pack into a mass of minimum volume and only a small quantity of liquid is needed to fill the voids between particles and there is just sufficient space to enable the particles to move past each other slowly. When the suspension is sheared rapidly the particles are forced out of their close packing and the void space is increased, i.e. system dilates. Such suspensions and deflocculated systems are best avoided by formulating the suspension so that the particles are slightly flocculated. Therefore dilatant types of materials are always rare in pharmaceutical and cosmetic industries.

Equation (3) above, does not hold for many emulsions and San grew et al (1961) proposed another equation to overcome some of the objectives of equation 3 as

$$S = \psi + \eta_{\infty} \dot{\sigma} - b_r C^a \quad \ldots\ 4$$

where ψ, η_{∞}, b_r and a are constant characteristics of a particular system. The term ψ, is the intercept of the stress axis of the flow curve at high shear rates and η_{∞} is the slop of the line. The yield value is $4 - b_r$, and the constant, a, is found to have a value of 0.001 for system he investigated.

(iii) Bingham Body

A Bingham or Plastic body (fig. 1.4 E) behaves like Newtonian except for the fact that the Newtonian or pseudoplastic bodies will flow under the application of the smallest shearing force, a Bingham material will fail to flow until a certain shearing stress has been applied and can be presented by equation

$$\frac{S - \psi}{\dot{\sigma}} = \eta_{plastic} \quad \ldots\ 5$$

where S, is the shear stress, $\dot{\sigma}$ is the shear rate, ψ is yield stress or yield value and the $\eta_{plastic}$ is the coefficient of plastic viscosity. Such

typical materials include concentrated suspensions of solids, ointments, bodied emulsions and gels.

(iv) The Yield Value

The rheogram of plastic body is linear over most of its length, corresponding to that of Newtonian, but, unlike Newtonian, it does not pass through the origin, instead, its linear portion intersects the horizontal axis (when the linear portion is extrapolated) at a point known as the yield value, ψ , i.e. a viscoelastic material from all intend and purpose. Specifically, many types of emulsion creams having 'body' including those in this work are of this nature. Others include certain ointments, suspension of zinc oxide in mineral oil, certain paints, inks, firm jellies and many cosmetic creams. The yield value is thought to result from the network of floccules that agglomerate or stick together forming a continuous but not orientated structure throughout the mass which is broken down as the material begins to flow, Martin et al (1964). Flow cannot take place until the applied stress exceeds the force of flocculation which causes the particles to adhere together. The importance of yield value can be appreciated in the ointments and creams which do

not drip from fingers, spatulas and knives but hold their shapes (elastic) until sheared by spreading pressure and if it is exceeded, it suddenly starts flowing (viscous) and spread.

The rheograms of certain materials can be more complex. Frequently, bulges and spur-like protrsions in the up curves do occur. The spur-like protrusions in the up curve is referred by Ober et al (1958) as 'T value', Levy (1962) referred to it as the Static Yield Value, the exaggerated yield value referred by Talman, Davis and Rowen (1968) or simply the maximum torque/sharing stress on the initial up curve, represents a sharp break-down point in the structure at a very low rate of shear. The 'T value' of Ober et al (1958) was found to be the key to the sustained action of their 40 - 70%w/v concentrated suspension of Procaine Penicillin G. The value was found to be directly related to the specific surface of the powdered penicillin used in the suspension. Preparations having no 'T value' do not give the sustained action of Ober et al (1958).

(v) Thixotropy

Thixotropy means time-dependent reversible flow behaviour. The types of flow considered above refer to equilibrium effect and therefore independent of time, Green et al (1949); Martin et al (1964) and Lenk (1978). Time dependence effect assume major importance when the system changes gradually rather than instantenously when a shear field is applied. It is otherwise referred to as 'an isothermal sol ⇌ gel reversible and comparatively slow transformation' and on standing of the material of a consistency lost through shearing. In pseudoplastic and plastic materials, a behaviour was seen to arise from the competition between the detachment of entanglement links tending to align themselves in the direction of flow among dispersed particles by shear, and the re-establishment of such links by Brownian motion tending to regenerate the structure. The rate of entanglement and randomization by Brownian motion is constant, while the rate of disentanglement and alignment increase with increasing shear, the balance between them shifts more and more to break-down as the shear is increased, thus the consistency decreases. This is because reduction

in interchain or interparticulate links result in smaller flow units and lower apparent viscosity and so the system adopts itself to a changing shear instanteneously such that equilibrium between bread-down and restoration of links at a new shear rate is easily reached, Scott (1945).

The extreme behaviour of thixotropy is the isothermal reversible sol ⇌ gel transformation produced by rest and by shear reversibly. Example of such materials can be seen in 8% w/w Sodium Bentonite gel. When prepared, it settles within an hour or two but can flow and be poured when stirred within minutes. Concentrated parenteral suspensions of 40 - 70° w/v procaine Penicillin G in water were found to have a high inherent thixotropy and were shear-thinning, Ober et al (1958). Corresponding dilute suspensions were less thixotropic. The greater the thixotropy, the lower will be the rate of settling of the suspended particles.

The rheograms of such material is of hysteresis loop. The apparent viscosity depends not only on the temperature, composition and rate of shear or stress, but also on the previous shear history

and time under shear, Houwink (1953) Green and Weltmann (1949), Fishcher (1950), Kostenbonder et al (1954), Mysel (1959) and Sherman (1970) (see figure 1.5).

The phenomena of thixotropy on molecular level seems to be caused by rupture of weak secondary bonds between molecules. These bonds must therefore vary in strength or distribution throughout the fluid so that a finite time is required to rupture them, usually, for a given shear rate, there is an appreciable number of bonds whose strength is very nearly that of the applied equilibrium stress so that the equilibrium is often approached asymptotically. The forces could propably be electrical in character in most cases or physical as in synthetic flocculants for example where points of attachment may vary in strength.

The opposite irreversible work-thickening or antithixotropy in which materials exhibits more resistance to flow with increasing time while subjected to steady-state shear is rarely encountered in pharmacy and of no interest to us and therefore will not be discussed beyond here.

Thixotropy is particularly useful in formulation of pharmaceutical creams and cosmetics. The fact that most emulsions are shear thinning may be of significance in the physical stability of the systems because a shear-thinning emulsion is definitely the consumers' standpoint particularly if the emulsion should have considerable body or consistency, and yet the product must pour readily from the bottle, be administered conveniently on spoon or be easily applied to spread on and adhere to the skin. A well-formulated thixotropic suspension will not settle out readily in the container, it will become fluid on shaking and remain so long for a dose to be dispensed and finally, will regain consistency rapidly enough so as to maintain the particles in a suspended state. A thixotropic agent such as gum, cellulose, synthetic emulgent etc. are incorporated into emulsions or suspensions to confer high apparent viscosity (body) which retards sedimentation or cream while the yield value prevents them all together. When it is desired to pour from container, it is shaken well, the agitation temporarily breaks down the thixotropic structure reducing the yield value to zero and lowering the apparent viscosity.

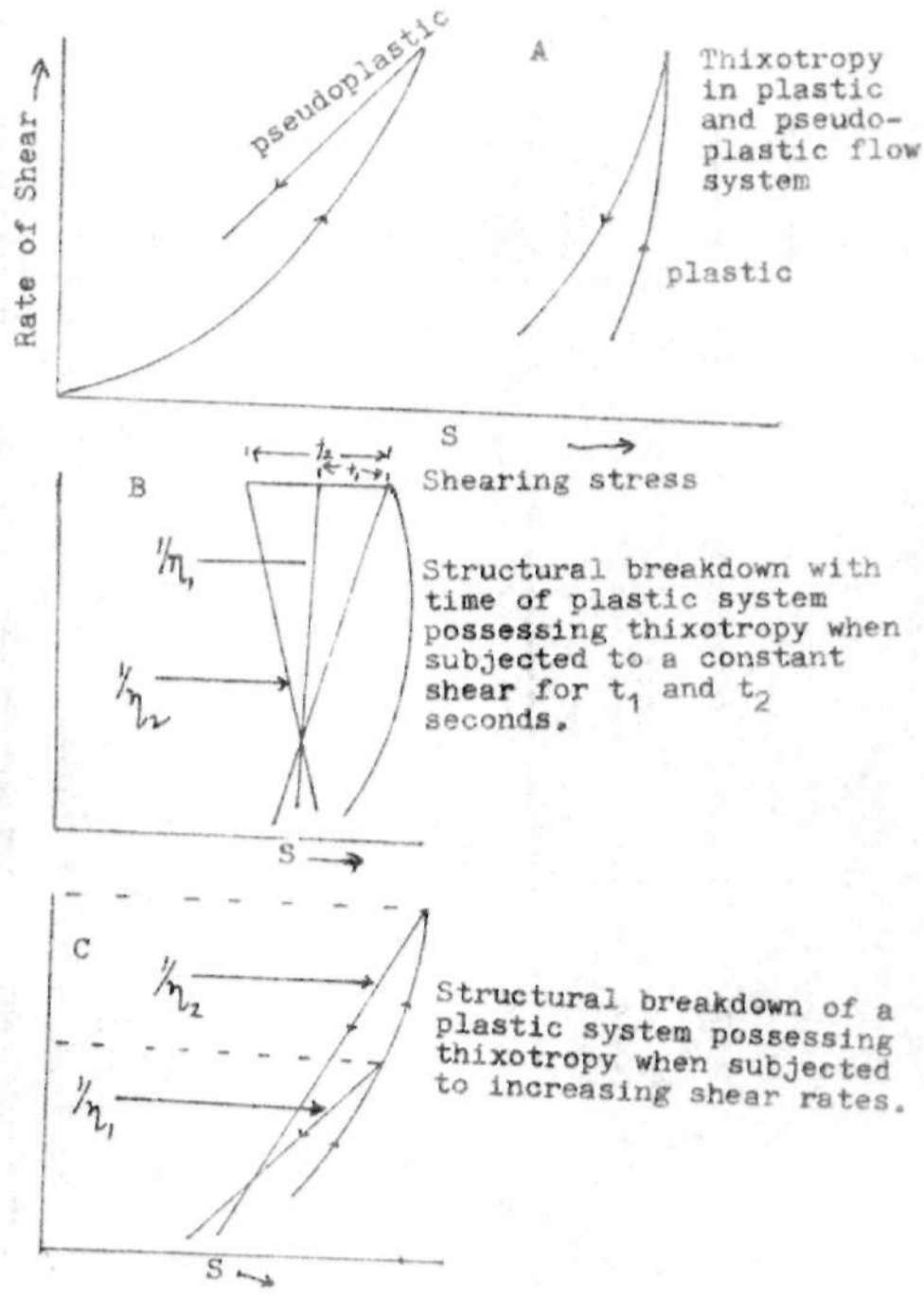


Fig. 1.5 (McKennel (1960))

Hysteresis loops are formed by the up and down curves of the thixotropic material when sheared to a certain maximum value progressively and allowed to deaccelerate to zero shear rate. The process is a dynamic one. There are several ways in which a quantitative measurement of thixotropy can be attempted. The most apparent characteristic in a thixotropic system is the hysteresis loop. The area of the loop has been proposed to be a measure of thixotropic break-down and can readily be obtained by means of planimeter, or other suitable technique.

For plastic bodies, the structural break-down with time at a constant rate of shear (fig. 1.5B) is based on such rheogram, a thixotropic coefficient B, the rate of break-down with time at constant shear rate, is calculated as follows:

$$B = \frac{\eta_{1\ plastic} - \eta_{2\ plastic}}{{}^{1}n\ {}^{+}2/t_1} \quad .... 6$$

where $\eta_{1\ plastic}$ and $\eta_{2\ plastic}$ are plastic viscosities of the two down curves calculated from equation (5), after shearing at constant rate for t_1 and t_2 seconds respectively. A more useful, though time consuming, method for characterizing

thixotropic behaviour is to measure rates of shear Martin et al (1964 b). Another approach is to determine the structural break-down due to increasing shear rate (fig. 1.5 C), two hysteresis loops are obtained having different maximum rates of shear v_1 and v_2. The thixotropic coefficient M, the lost in shearing stress per unit increase in shear rate

$$M = \frac{2\ (\eta_1 - \eta_2)}{{}^{1}_{n}\ (v_2/v_1)^2}\ (\text{dynes sec/cm}^2) \quad ..7$$

The rheograms of certain thixotropic materials can be more complex than those referred in the text. Frequently, the loops contain bulges or spur-like protrusions in the up curve (fig. 1.6) Martin et al (1964 b).

In rheograms of pseudoplastic and plastic materials, the shear stress may be seen to decrease even with increase shear rate i.e. the shear stress increases less than proportionate with increasing shear rate (fig. 1.6 a). Actually the shear stress should never decrease with increase shear rate but in practice atimes it does particularly in materials with low yield values. This is due to an easily explained artifact.

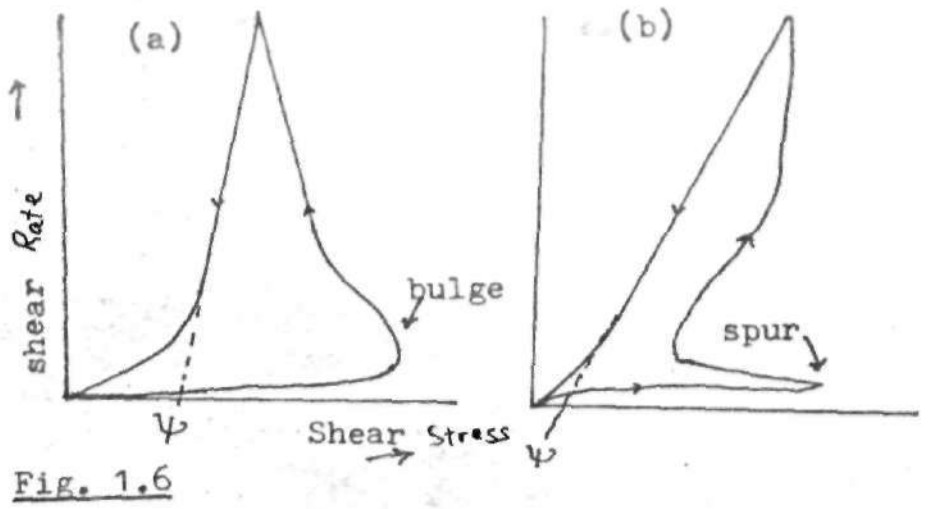


Fig. 1.6

Typical rheogram of an oil-in-water cream showing the bulge (a) and spur-like protrussion (Abubakar, 1981)

It simply means that the maximum shear rate at which a meaningful result can be recorded has been exceeded; or 'voids' might have appeared in the material, or it might have 'cavitated', 'split' or 'fractured'. At this point, the laminar or stream-line flow has seized and has given way to 'turbulance' or 'plug' flow', Van Wazer (1963) and Davis et al (1968). In turbulance flow, the internal motion of the fluid is not smooth but includes many 'whorls' and 'verticles' i.e. many types of shapes. In practice, the on-set is signalled in a flow curve by the .

bending of the up curve towards the stress axis (figure 1.6 (a)). The lower the resistance of a material to flow the more easily turbulance can set in, Barry and Saunders (1971), Davis et al (1971), and Wood and Catacalos (1963). In other words, the apparent rate of shear is diminished by turbulance to a value below that expected for laminar flow at a given applied shearing stress. 'Plug' flow occurs because the material moves in 'chunks' or as a plug rather than laminar motion. That is why in most cases the yield value is only obtained by extrapolating the linear portion of the stress axis (figure 1.3). Lenk (1978) has summed up the causes of flow inhomogeneity as to be due to the presence of two or more phases which matually interact such as to produce local perturbations in the strem lines. These may be due to interfacial forces, hydrogen bonding or other molecular interactions.

5. The aim of this work:

The aim of this investigation is to formulate a suitable oil-in-water cream base for incorporation of 1%w/w Clotrimazole that can be able to withstand tropical climatic conditions rheologically using cetostearyl alcohol/cetyltrimethyl Ammonium Bromide

as mixed emulsifier. In all the emulsified pharmaceutical and cosmetic creams that the author is aware of, the bases form between 95 - 99 percent of the entire dosage form. It is imparative therefore to assume that the small amount of the active ingredient in formulation will hardly or not at all affect any of the rheological properties of the formulation except where incompatabilities occur. To this end, a macroscopical means of examination and continuous shear viscometry will be used. The influence of such mixed emulsifier concentration and the alcohol/surfactant ratios on the viscoelastic properties of such creams will be investigated as they are affected by temperature fluctuations.

Such formulation, it is believed, will help in no small way considering the range of temperature variations such products can be subjected to in a country like Nigeria where the temperature fluctuation may be so great considering the adverse effect temperature fluctuation may have on the physical stability of emulsion creams.

CHAPTER 2

Materials and Methods of Investigations

1. Materials

Cetyltrimethyl Ammonium Bromide (CTAB) (B.D.H.) powder

$CH_3(CH_2)_{15}(CH_3)_3\overset{+}{N}.\ \overset{-}{Br}$

Mol. wt. 364.46

Assay - 98.93% calculated as alkyltrimethylammonium bromide $C_{17}H_{38}H.Br$ (Martindale 27th Ed. 1977)

Official requirement - Not less than 96%

1% solution in water has pH of 5.6. Official pH 5-7.6 (Martindale)

2. Cetostearyl Alcohol (also called cetyl alcohol)

flakes (B.D.H.). Mixture of chiefly stearyl and cetyl alcohols. Solidifying point = 46° - 47° (capillary tube method).

Official solidifying point requirement = 45° - 53° (B.P; B.P.C. 1973).

3. Liquid Paraffin (East Anglia Chemicals)

Mixture of liquid hydrocarbons
Viscosity 20° = 0.39 Poise or 0.44 Stokes

Based on castor oil 9.86 Poise as standard.

26° = 0.31 Poise based on water at 0.01 Poise as standard Oswald viscometry.

4. White Soft Paraffin (B.D.H.)

A bleached semi-solid mixture of hydrocarbons

melting point = 42° - 48°

Official melting point requirement - 38° - 56°
(B.P; B.P.C. 1973)

5. Citric Acid Analar (Hopkin & Williams) Crystals

$HO.CO\ CH_2.\ C(OH)(COOH)\ CH_2COOH.H_2O$

Mol. Wt. 210.14

Melting point = 56.5 - 57.0°

Assay (acidimetric) = 99.7%

Official requirement = 99.5 - 101.0%
(B.P. & B.P.C. 1973)

6. 4-Chloro-m-cresol crystals (B.D.H.)

or (2-chloro-4-hydroxytoluene)

Cl. $C_6H_3(CH_3).OH$ Mol. Wt. 142.59

Melting point - 64° - 65°

Official melting point requirement = 64° - 66°

Assay - 98.7%

requirement - 98.7% minimum content
(Manufacturers)

7. Sodium Acid Phosphate Crystals (M & B)

(Sod. Dihydrogen Phosph.)

$NaH_2PO_4 \cdot 2H_2O$ Mol. Wt. 156.01

Assay = 98.8% as $NaH_2PO_4 \cdot 2H_2O$

Official requirement = 98.8% minimum (Manufacturers)

" " Not less than 98% as $NaH_2PO_4.2H_2O$ (B.P. 1973)

8. Water Mol. Wt. 18.0

H_2O mains water distilled from all glass still was used throughout this work.

9. Castor oil (Lederle)

Fixed oil containing about 80% of the triglyceride of ricinoleic acid.

Density - 0.96 gm/ml at 20°

Viscosity at 20° - 9.86 Poise (standard)

10. "Canesten Cream" - (Bayer

Batch No. OU 564 H

Date of manufacture - Not stated

Active ingredient 1%w/w clotrimazole in inert cream base (o/w).

A. Melting Point Determination

Capillary tube method was used where applicable for the determination of solid materials. The results represented the mean of at least three readings. The solidifying temperature of white soft paraffin was determined by the method III B.P. 1973.

Results

The results obtained are all in agreement with the official requirements of the B.P. (1973) or the manufacturers' specification.

B. Assay Determinations

All assays where applicable were carried out using volumetric titration or any suitable assay method in any of the official compodium.

C. Viscosity Determinations

The viscosity of liquid paraffin was determined by Ostwald viscometry by comparism with the viscosities of water at 20^{o} - 0.01 Poise, standard castor oil at 20^{o} - 9.86 Poise and at 27.0^{o} - 5.68 Poise.

Solubility Determinations

Both the synthetic and the analytical techniques have been used in the investigation of the various systems, (Gbefwi, 1978).

D. The Synthetic Method

Basically synthetic method of solubility determination involves the addition of one component, in small increments, to an appropriate quantity or quantities by weight of one or more components as the case may be, placed in the small glass sample bottles. The phase changes and the equilibrium state being determined visually at 37^{o}. This

temperature of 37° was chosen because the water soluble components are added to the warm aqueous phase in the manufacture of creams. In case where equilibrium situation was not very clear, the systems were kept for 24 hours at 37°. This method was adopted to systems of solid in liquid and liquid in liquid.

B. The Analytical Method

This involves the quantification by weight of each component in each phase after the attainment of equilibrium. In systems containing two or more phases, the tubes could be centrifuged. The upper phases were first removed by using syringes and after 'complete' removal, the immediate lower phase was treated likewise. The U.V. spectrophotometer with methanol as the solvent and blank was used for analysis (Gbefwi, 1978), of the surfactant content. For liquid paraffin

extinction of 1 cc layer of 2.0% w/v solution of trimethylpentane, absorption range of 240 - 280 mu was used and 0.1% w/v of the same solution was used for white soft paraffin analysis viz. B.P. (1973).

Results of Solubility Determinations:

Synthetic Method

The results obtained are shown in Table II - 1.

a. Cetyltrimethyl Ammonium Bromide:

i. In water - was found to be soluble in all proportions with the formation of clear solution and milky solution formed upon increase in the concentration of surfactant up to 50 - 50% w/w.

ii. In liquid paraffin -

Systems with surfactant content forming milky solution upon frequent shaking for several hours. The resultant mixtures with increasing surfactant concentration gave a solid and co-existent milky liquid. The solubility of surfactant in the liquid paraffin was about 1 part surfactant to 10 - 11 parts liquid paraffin at this temperature 37° after frequent shaking.

b. Cetostearyl Alcohol

The results obtained are shown in table II - 1. The alcohol was found to be practically insoluble in water at all proportions and also insoluble in liquid paraffin at all proportions even with frequent shaking. It however dissolved in all proportions of liquid paraffin and soft paraffin when they are all melted i.e. at temperature of above 42^{o}.

c. Liquid paraffin - (also soft paraffin)

- in water - practically insoluble in all proportions
- in soft paraffin - miscible when melted only
- in cetostearyl alcohol - immiscible in all proportions except when melted.

d. Sodium Acid Phosphate, Citric Acid and Chlorocresol Systems.

- All soluble in all proportions in water but chlorocresol dissolved only in 260 parts water.
- Practically they are all insoluble in liquid or soft paraffin.

Table II - 1 Solubility Result - Synthetic Method 37°

System	Phase(s)	Solubility	Literature
a) CTAB			
- in water	L	soluble in all proportions up to 50 - 50% w/w	1, 2, 4, 5
in soft paraffin		insoluble in all proportions	1, 2
b) Cetostearyl alcohol in water	L + S	Practically insoluble	1,2,3,4 & 5
c) Liquid in soft paraffin	L	Soluble in all proportions when melted	
in water	L + L	Immiscible in all proportions	1,2,3 & 5
in CTAB	L + S	Dissolved only less than 10% of CTAB	
in cetostearyl alcohol	L + S	Dissolved only when melted	
d) Citric Acid, Sodium Acid Phosphate and Chlorocresol		Chlorocresol dissolved in 260 parts water	
in water	L	soluble in all proportions with shaking	1,2,3,4 & 5
in liquid paraffin	L + S	Practically insoluble	

References

L = Liquid phase clear or milky

S = Solid phase

1 = British Pharmacopoeia (B.P. 1980)

2 = British Pharmaceutical Codex (1973)

3 = European Pharmacopoeia (1973)

4 = European Pharmacopoeia (1977)

5 = Martindale. The Extra Pharmacopoeia 27th Edition.

Results of Solubility Determination by Analytical Method

Analytical methods were used only where the synthetic method was found to be insufficiently accurate or where no acceptable data was available in the literature. This method was adopted for systems of CTAB in water and in liquid paraffin since the soft paraffin behaves as the liquid paraffin only when melted.

a. The systems CTAB in water

The results obtained are shown in table II - 2. The soap content was analysed by U.V. spectroscopy. The soap content of 60% in 40% water was detected at the temperature. The result conformed closely to the synthetic data.

b. The system CTAB in liquid paraffin

The soap content of up to 15% in liquid paraffin were made and equilibrated at 37^{o} with frequent shaking for several hours. The resultant mixtures gave a solid and co-existent liquid. U.V. spectrophotometric analysis showed up 10.5% of the soap in the solution phase.

c. The systems Cetostearyl alcohol in water and in liquid paraffin

The systems were analysed by U.V. spectrophotometry. The results showed no trace of alcohol in either the water or paraffin liquid phases.

Table II - II: Result of Solubility Determination- Analytical Method *CTAB*

	System	Phase(s)	Solubility	Technique
A	CTAB - in water	L	soluble in all proportions up to 50 - 50% w/w	U. V
	— in liquid paraffin	L. S.	10.6% w/w	U. V.

Ferrenti-Shirley (Viscometer)

General Description -(Ferrenti-Shirley Viscometer Operating Manual).

Essentially, Ferrenti-Shirley viscometer (see figure II - 1) consists of a stationary flat plate lower (10), and a rotating conical disc or cone (2), which is driven by a variable speed motor (14). through a gear train (15) and torque spring (4). The tortion due to viscous drag is measured by a potentiometer (6) on the spring which sends a signal to an X -Y recorder (Reference McKennel Ltd. (1960)) or to a simple dial indicator. The motor is a d.c. motor-generator which feeds back a voltage directly in proportion to the rotational velocity. This voltage is fed into an amplifier unit and compared against a stable reference voltage. The potential difference after amplification is fed back to the motor thus a velocity seruo-mechanism which produces a speed virtually independent of the viscous drag on the cone. A tachometer is alternatively fitted to the d.c. motor-generator and it feeds a signal to the recorder enabling plots of r.p.m. on the Y axis and torque on the X axis of the recorder.

In addition, the control unit can generate a voltage increasing linearly with time which is applied to the motor via the amplifier - thus a programmed accelaration and decleration of anguler velocity can be determined. Additionally, a rapid full-scale sweep of the speed range may be achieved in about one second, for example while accelerating to a specific cone velocity before commencing the test. Thus slow or fast hysteresis loops can be obtained.

The bottom plate is movable and is provided with an electrical connection that indicates on the control and indicator unit when the plate is just touching the apex of the cone. This setting is achieved reproducibly to within 0.0001 inches by means of a micrometer (11) adjustment at the base. Once set and locked, the plate and cone can be separated for cleaning and addition of the sample and returned to this position without subsequent adjustment. The plate is fitted with a circulating water (17) system and has three thermocouples (16) embedded therein which are in direct contact with the test fluid in the gap which permits temperature measurement of the sample to be made during the run.

There are three cones which operate for the approximate ranges of viscosities of the test fluid viz. radii 3.5 cm, 2.0 cm and 1.0 cm termed large, medium and small cones respectively. The large cone is usually employed for low viscosity fluids (1 - 10 poise) and the small cone is used for fluids of about 25 poise. The nominal angle of the standard cones is 20 minutes ($\frac{1}{3}^{o}$) or approximately 0.006 radians.

a Measurement Procedure

A suitable cone is selected and then fitted to the cone flange. A spirit level is placed on the plate of the measuring unit and the unit levelled by means of two levelling screws located on the front of the base plate. The water bath is actuated and a few minutes are allowed for the water to stabilise at the required temperature.

Cone-plate Setting and Adjustment

In Ferrenti-Shirely, as in all cone-plate viscometers, the position of the cone with respect to plate is critical for a reproducible accuracies. However, once set for a particular cone, the plate can be raised or lowered to the same position.

KEY

1	Cone Spindle	
2	Cone	
3	Driving Spindle	
5	Bridge Housing	
4	Torque Spring	Torque Dynamo-meter
6	Potentiometer	
7	Wiper for Potentiometer	
8	Slip Rings	
9	Slip Ring	
10	Plate	
11	Micrometer	
12	Nut	For raising plate
13	Screw	
14	Driving Motor	
15	Gearing	
16	Thermo-couple	
17	Water Jacket	

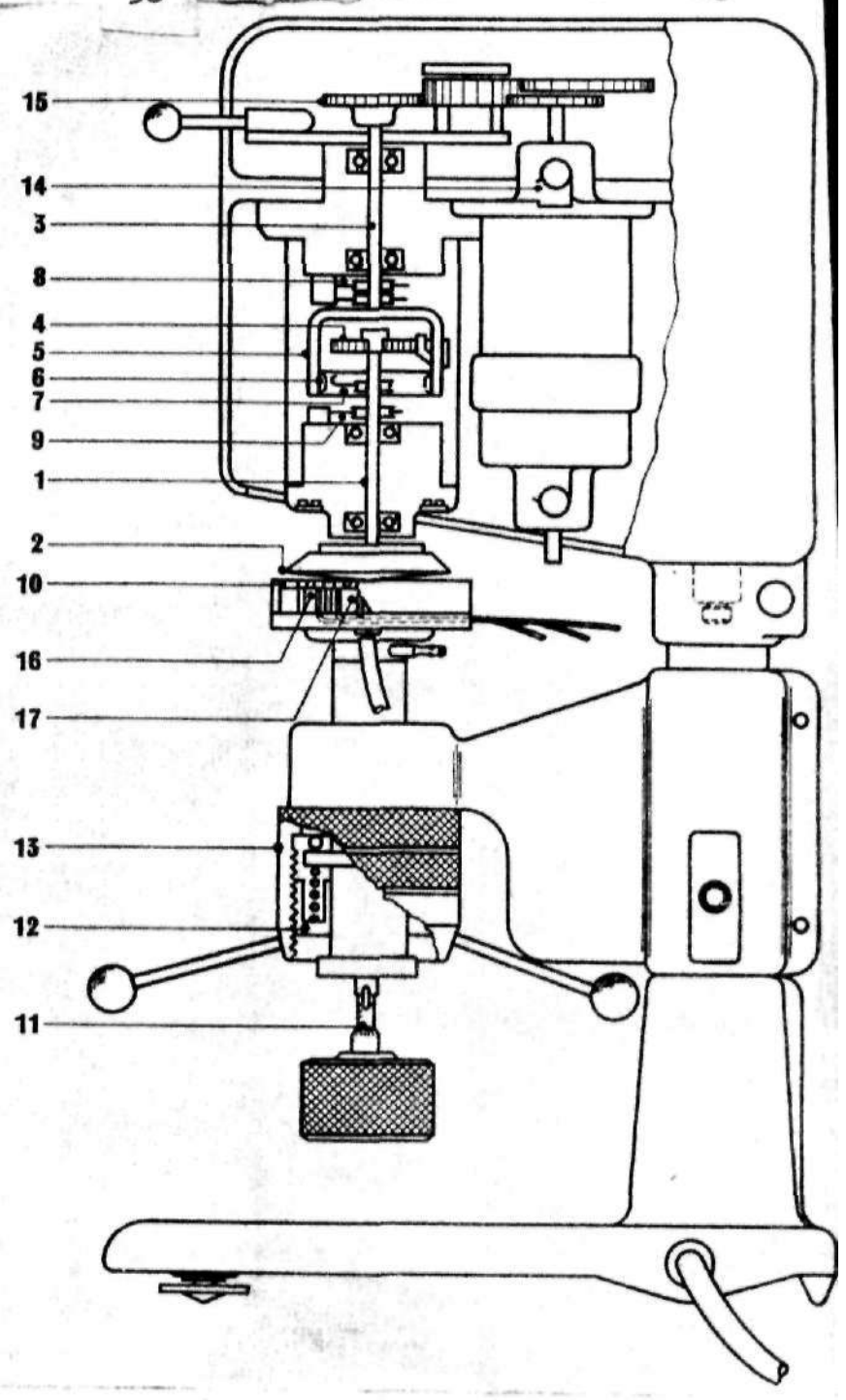


Figure II - 1 The schematic Diagram of the Measuring Unit of a Ferrenti-Shirley Viscometer.

During measurement, the correct position of the cone is maintained throughout changes of ambient temperature by the cone and plate setting circuit. The initial setting should be precise. The apex of the cone should just touch the plate. The lamp on the front panel will light when the plate is just touching the cone, indicating that the heater in the measuring unit panel is switched on. When the plate is not touching the cone, the heater is switched off allowing the plate to move back to the cone. The cone and plate thus move apart together in a cyclic manner and an indication of the operation is provided by the switching on and off of the lamp. A correct setting of the micrometer is indicated by the light cycling on and off within few seconds.

The desired speed is then selected and the torsion is noted on the indicator unit or on the recorder, as desired. The speeds may be manually selected or programmed. Since the rate of shear is directly proportional to r.p.m. as indicated by the tachometer signal on the recorder, programming will give a continuous plot on the recorder of stress versus shear rate.

The X « Y recorder can also plot the time dependent effect i.e. the hysteresis loop from zero shear rate to a predetermined maximum and then returned to zero on acceleration-deccelera-tion programme determined from a range of 10 - 600 seconds in eight possible rates. Non-Newtonian behaviour is best plotted on the X - Y recorder and apparent viscosities are obtained directly from the plots.

The relationship for the three standard cones between r.p.m. and rate of shear is a simple factor of about 18. Thus at 1 r.p.m. the rate of shear is about 18.0 sec . The maximum measurable torque is 1.2 x 10 dynes /cm.

Since measurements and calculations involves mathematical calculation from the dimentions of the plate and cone which are constant for a particular cone; the formula • below allows the calculations:

$$\mathbf{n} \cdot \frac{3 <<T}{2\ TTR?/2}$$

whereby is the viscosity

<*/ * angle of cone (i)

R = radius of the cone (cm)

T = Torque Spring constant = $\frac{\text{Max. Torque}}{£\text{ocT}.....}$

angular velocity (radius/sec)

The stress is equal to $\frac{5\ T}{211\ R^3}$

The shear rate $(\frac{dv}{dr} = \frac{\Omega}{r})$

The Ferrenti-Shirley has a small cone angle ($\alpha < 0.3^{o}$) the rate of shear across the conical gap may be considered constant and therefore gives directly the true rate of shear.

The checking of cone constant is essential and can be done experimentally.

$$\text{The Cone Constant } C = \frac{\text{Viscosity of Standard (Poise) x R.P.M.}}{\text{Instrument Reading x Scale Reading}}$$

The shear stress constant can be obtained from the equation: $\tau = \frac{3\,T}{2\,\Pi\,R^{3}}$ dynes/cm^{2}

The Shear Rate constant is calculated from $\frac{\gamma}{C}$ where γ and C are as above.

c. Calibration of Cones

The cone to be calibrated was fitted and the viscometer set-up as follows:

Speed dial set to zero

Function switch set to manual

Power put on the ON position

The MOTOR put on the MOTOR ON

The measureing unit started to rotate and was then set to stationary position by adjusting the MOTOR ZERO control.

The gear lever was set to high gear position thus giving a normal (XI) speed when the tufol pinion A was engaged.

The plate was lowered, cleaned and sufficient castor oil standard fluid was placed to fill the gap between the cone and plate. The plate was slowly raised into the operating position. The range switch was set to X4. The speed control then turned to give a progressive speed of 5, 10, 15 ..... 50 (at 5 R.P.M. interval) and the respective reading on the instrument recorded until the maximum desired speed was reached. The cone speed was reduced in same increments and the readings also recorded for each speed until the cone speed is zero again. The plate was then lowered slowly for the cleaning of the sample.

During the measurement procedure, a water bath at control temperature was run through the measuring unit and an allowance of three minutes was given before reading was taken to allow each sample to stabilise to measurement temperature of the water bath.

Standard Castor oil viscosity = 9.86 Poise

at 20°

at 27° = 5.85 Poise

Gear normal speed - X1 tu fol pinion in A position

Range/Scale - X 4

Results - See Tables II - 1, 2 & 3

Cone size - 7.0 cm diameter

Cone constant - Table II - 1 & 2 = 1.25 at 20°

Cone constant - 1.27 at 27°

Mean. 1.26 (Manufacturers' gave 1.26)

Medium Cone - 4.0 cm diameter Table II - 3

Cone constant at 20° = 6.89

(Manufacturers' 6.88)

Castor oil at 20° - 9.86 Poise

Conclusion

The viscosity constant for the large cone (7.0 cm diameter) was found by experiment to be 1.26 as the same given by the manufacturers. For the medium cone (size - 4.0 cm diameter) the viscosity constant of 6.89 was found as against 6.88 given by the manufacturers giving a difference of 1/690. The shear stress and shear rates constants are given as:

CALIBRATION EXPERIMENTAL RESULTS

Table II - 1: Cone size - 7.00 cm diameter Castor oil 20° 10.3 Poise

R.P.M. ⟶	5	10	15	20	25	30	35	40	45
Reading Up	10.25	20.60	30.76	40.8	51.10	62.20	72.8	81.7	91.1
Reading Down	10.20	20.55	30.50	40.8	51.00	62.10	72.6	81.7	91.1
Mean Reading	10.23	20.60	30.60	40.8	51.05	62.15	72.7	81.7	91.1
Constant C	1.26	1.25	1.26	1.26	1.26	1.24	1.24	1.26	1.27

Range x 4 Mean Cone Constant C = 1.25

Table II - 2: Cone size - 7.0 cm diameter Castor oil at 27° 5.85 Poise

R.P.M. ⟶	10	20	30	40	50	60	70	80	90
Reading Up	11.66	22.66	34.30	46.30	57.10	67.5	80.6	90.1	
Reading Down	11.41	22.30	34.00	46.00	56.90	67.30	80.0	90.1	
Mean Reading	11.50	22.45	34.15	46.20	57.0	67.40	80.0	90.1	
Constant C	1.27	1.30	1.27	1.27	1.28	1.30	1.30	1.	

Range x 4 Mean Constant C = 1.27

Overall mean C = 1.26 (Manufacturer's 1.26)

Table II - 3: Cone size - 4.0 diameter Castor oil at 20° 10.5 Poise

R.P.M. ⟶	5	10	15	20	25	30	35	40	
Reading Up	7.60	15.00	22.60	30.30	37.60	45.00	51.50	58.80	
Reading Down	7.30	11.80	22.40	30.10	37.40	44.80	51.30	58.80	
Mean Reading	7.45	14.70	22.50	30.20	37.50	44.90	51.40	58.80	
Constant C	6.90	6.9	6.85	6.81	6.85	6.88	7.0	6.89	

Range x 1 Mean Cone Constant = 6.89 Cone 4.0 diameter (Manufacturer's 6.88)

$$\text{Shear stress constant } \gamma = \frac{3T}{2\pi R^3} \text{ dynes/cm}^2$$

$\therefore \quad \gamma = 22.765$ for Cone size 7.0 cm diameter

similarly $\gamma = 122.021$ for cone size 4.0 cm diameter

Shear Rate Constant = a roughly simple multiple of 18 - (Given)

Large cone = 18.068 sec^{-1}

Medium cone = 17.692 sec^{-1}

d. To Find the Operating Limit Parameters

The operating limits parameters referred here are, the sweep time, shear rate, scale expansion, X - Y recorder sensitivity range recorder Cal/Ver out position, and the recorder Filter/Filter out position.

Cal/Var = Calibrated/Variable mode of operation.

Introduction

With the Ferrenti-Shirley instrument, different combinations of sweep times and maximum shear rates will affect the shape of the resultant hysteresis loop and make comparism difficult. A decrease in all the measured parameters i.e.

the yield value, thixotropy and plastic viscosity, occur with increase in sweep time, Davis et al (1968). The acceleration of the cone at different sweep times will affect the loop size and shape by several mechanisms (a) the yield value of a material is not independent of time and (b) static yield value of a material is a function of rate of the strain and is associated with viscoelasticity and retardation behaviour, McVean & Mattock (1961). At low sweep times the apparatus will constitute an oscillatory system, introducing effect due to inertia and the tortional stiffness of the spring Cheuf (1965), Ferry (1961) and Van Wazer et al (1963).

The scale expansion will only affect the reading scale, a small expansion scale e.g. X 1 will give a large reading while high expansion of e.g. x 6 will give small reading which is convenient for a more viscous fluids. The X - Y recorder manouver will similarly affect the sensitivity of the instrument and therefore affect the size and smoothness of the rheogram.

With all these variables, it is evident that operating limits are necessary for comparative work. An official cream with most physical characteristic similar to the type to be used in

our investigations will therefore be an appropriate test sample to find these operation limits and therefore an aqueous cream B.P.C. 1973 was used. It was prepared by fussion method stirred with hand stirrer and allowed to cool at room temperature (27^{o}).

To find the operating limits

Various experiments were conducted and the corresponding results and comments were as under -

Temperature - 270^{o}

Cone size - 4.0 cm diameter

(a) Sweep time - 240 seconds

X - Y recorder sensitivity - 10 mV both axes

R.P.M. - 200

Result - rheogram

X - axis height (shear stress) - 12cm

Y - axis height - 25 cm

Hystresis loop - large

Conclusion - the X- axis is short

Y - axis is too long.

(b) Sweep time - 240 seconds

R.P.M. - 200

Sensitivity - 2.5 m.V.

2.5 m.V - X axis

Results

X - axis - (shear stress) 25 cm

Y - axis - (shear rate) - limit exhausted i.e. the upper limit of paper was reached before shear rate max. was reached.

Rheogram is fine but shear rate was too much.

Hysteresis loop - large.

Conclusion

The X-axis sensitivity is suitable.

(c) Sweep time - 480 seconds

R.P.M. - 200

Sensitivity - 25 mV

Results

Rheogram fine with both axes correct

Hysteresis loop - too large

Conclusion - the sensivity of 2.5 mV on both axes was suitable.

(d) Sweep time - 240 seconds

R.P.M. - 100

Sensivity - 2.5 mV both axes

Cal/Var - cal.

Results - Hysteresis loop wide. Both axes reached a reasonable height and distance

Conclusion

These parameters are good 2.5 m Volts sensitivity. R.P.M. accepted but sweep time gave too large hysteresis loop area.

(e) As (d) above but sweep time changed to 120 seconds.

Results

The rheograms are good and reproducible.

Overall Results and Conclusions

The rheograms with medium cone showed that they can be reproduced and good for comparative work; but all rheogram curves were not smooth.

Similar experiment with large cone (7.0 cm diameter) produce a smooth, reproducible and comparatively medium size rheogram. Therefore these parameters are accepted with large cones.

Speed - 100 r.p.m.
Sweep time - 120 seconds
X - Y recorder

Sensitivity - 2.5 m.V. - both axes
Cal/Var - to cal. on both axes
Filter/Filter out - to filter on both axes

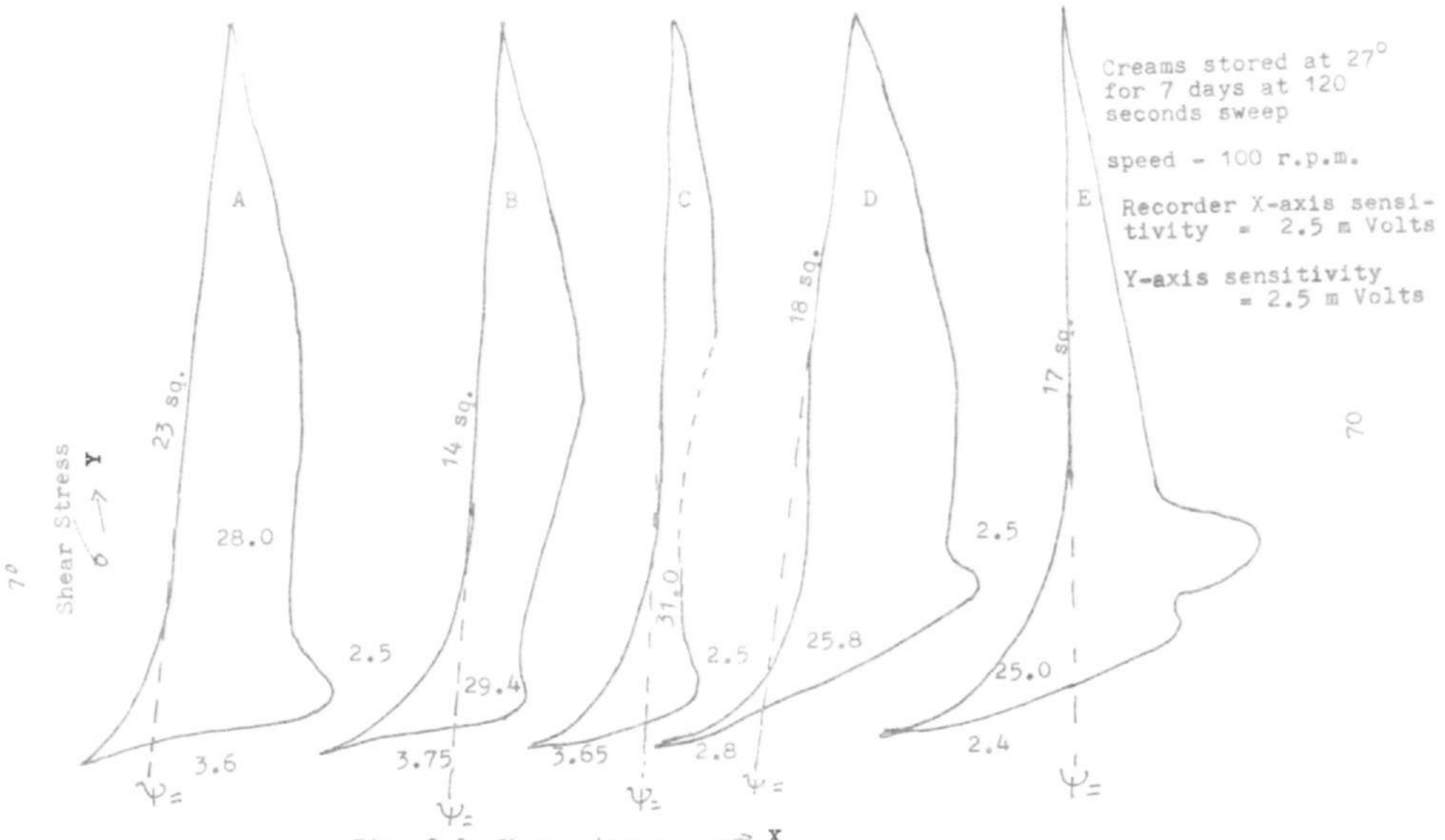


Fig. 2.2 Shear stress ⟶ X

Rheograms of formulations A - E of 9% mixed emulsifier showing the smooth, reproducible and comparatively medium sizes.

(See figure II - 2)

Similar experiments conducted at different temperatures 20° - 45° showed that these operating limits were still acceptable and were good for comparative work.

3. Method of preparing cream bases

(a) Introduction

Considering the number of variable factors affecting the ultimate physical stability of emulsion cream, it becomes necessary to state the experimental procedure adopted in the preparation, storage and other factors for reproducibility.

(b) Preparation of Creams

Tables II - 4 and 5 are the general formula for making the cream bases. Fresh samples of each material was used and taken directly from the containers and at no time a portion is returned into the container.

The creams were prepared by melting together of the weighed CTAB. powder, the alcohol flakes, the liquid paraffin and soft paraffin with stirring. The citric acid, the sodium acid phosphate and the chlorocresol were dissolved in the previously measured and warmed freshly

distilled water. The aqueous phase was warmed on a water bath to about the same temperature to that of the oil phase, 60 - 70°. The aqueous phase was then added to the oily phase with stirring while still on the water bath. The hot 'course' emulsion was transferred to a Q.P. hand homoginiser and homoginised about two passages by the end of which the creas was solidified and can pass no more. The finished emulsion was allowed to stand to room temperature before storage.

Storage

Each sample was filled into fine glass beakers of about 250 cc capacity, covered and sealed with aluminium foil and adhesive to make it 'well-closed' so that an adequate protection against microbial or physical contamination is minimised. One sample of each formulation A to E and of each concentration 7 to 11% was kept in an electrical oven at temperature 27°, 37° and 45° for 7 days, those for 10° and 20° were stored in a cooled incubator for 7 days. The 7 days period is allowed because it is believed that for ionic emulsifying agents like the CTAB, equilibrium will be attained within this period and that relapsing due to aging has not started, Barry and Saunders (1970, 1971), and Barry (1969) and Barry and Shotton (1968).

Table II - 4: General formula adopted for the preparation of cream bases.

Material	Concentration % w/w
Surfactant. Cetyltrimethyl Ammonium Bromide (CTAB) Cetostearyl alcohol	7, 8, 9, 10 & 11 at various ratios of alcohol/CTAB.
White so-ft paraffin	15.0
Liquid paraffin	6.0
Chlorocresol (crystal)	0.1
Sod. Acid Phosphate (crystal)	2.5
Citric Acid	0.5
Water	to 100.0

Table II - 5: Cream base formulations, alcohol/surfactant (CTAB) ratios

FORMULATION	Alcohol	Surfactant	Ratio
A	11 parts	1 part	11:1
B	10 parts	1 part	10:1
C	9 parts	1 part	9:1
D	8 parts	1 part	8:1
E	7 parts	1 part	7:1

1. Macroscopial Examination

Samples were examined macrosopically as regard to their appearance and feel immediately after preparation and at the end of storage at various temperatures.

2. Rheological Examination

Continuous shear method

Each cream sample was examined at each temperature using Ferrenti-Shirley cone and plate viscometer equiped with a maximum torque spring of 1.175×10^6 dynes/cm^2, a large cone of size 7.00 cm diameter with an apex angle of $\frac{1}{3}^o$, an X - Y recorder and a constant temperature bath. An external water bath was connected to feed the constant temperature bath of the machine while direct tap water was run as cooling system for temperatures 37^o and 45^o. Each sample to be measured was taken from the centre of the content after the upper skin layer was swept. No part of the sample was returned to the container once taken out. The instrument was set at 100 r.p.m. speed (i.e. 1806.8 sec^{-1} shear rate) and an expansion of x 6 was used and a sweep time of 120

seconds. An allowance of 3 minutes was given for each sample to stabilise to temperature in the measuring gap.

Analysis of Results

Each experimental point represents an average of at least three readings of different samples.

1. Readings - an instrument reading taken directly at the apex of the shear rate. This may not necessarily be the maximum attained.

2. Shear stress, S - a direct result of the reading above at the end of maximum shear rate.

$$\text{Shear stress} = \text{Reading} \times \frac{\text{Shear stress constant}}{\text{Expansion}}$$

or Reading x 22.765 x 6.

3. The Yield Stress or Yield Value, Ψ

This was read by extrapolation of the straight down curve of the rheogram to the shear stress axis at zero shear rate. Measured with a ruler in cm and computed to appropriate shear stress by comparism in proportion with the shear stress attained.

4. The Apparent Plastic Viscosity, $\eta_{app.plastic}$ as in equation 5.

$$\eta_{app.\ plastic} = \frac{S - \Psi}{\sigma} \text{ poise}$$

$$\text{or} \quad \frac{S - Y}{1806.8} \text{ poise}$$

5. Thixotropy - Ref. Levy (1962)

The thixotropic break-down was given by a measure of the hysteresis loop area of the up and down curves of the rheogram. The method adopted was such that an area equal or greater than half cm^2 from a graph paper was counted as whole while one less than half was not. 1 cm on the shear rate axis represents 7.2 sec^{-1} and 1 cm on the shear stress axis represents 342.4 $dynes/cm^2$ accordingly, a thixotropic area of 1 cm^2 was equal to 2465.3 G/cm. sec.

Examination of Sample Cream

A sample cream of Clotrimazole (Canesten, Bayer) as 1%w/w in water miscible base was squeezed out of the tube into a 250 cc size beaker, covered with aluminium foil, sealed

and stored at various temperatures as the sample formulations above for 7 days. It was then subjected to the same experimental exercises as the samples.

Batch Numbers - OV 561 H
OV 562 H
OV 563 H
OV 564 H
OV 565 H

Expiry date - Not Stated

Date of Examination - 17/03/82

CHAPTER 3

Results

1. Macroscopical Examination

a) Appearance

Immediately after preparation, emulsion creams were all fluid semi-solid and increase in consistency to soft semi-solid when allowed to stand at room temperature for up to 2 hours. The emulsions were all white, glossy, smooth textured soft-solid. The glossiness decreased with mixed emulsifier concentration. On storage for 7 days the glossiness also reduced slightly with age. All formulations stored at 10^{o} after 7 days were gritty and appeared dried due probably to coalescence of oil globules and particles growth. A decrease in consistency was observed with increase in temperature in all formulations stored at 20 - 45^{o} but appear gritty and look less consistent at lower temperature below 20^{o}.

b) Feel Sensation

Feel sensation described by Barry and Grace (1972) and Barry and Meyer (1973) as the sensation on the skin during spreading of the cream and does not include the initial feel

sensation on skin or the final impression due to residue on the skin. A slight increase in consistency was observed with increase in emulsifier concentration but a decrease with rise in temperature. Not much difference was detected between formulations except for the facts that formulation E (Table III - 5) was always more vulnerable to temperature variations than the rest.

c) Commercial Clotrimazole Cream

The appearance of Canesten cream just after extrusion from the tube was white and glossy, much whiter than the creams prepared in this laboratory by about one and a half times due simply to smaller size of the oil globules produced as a result of more efficient homogenisation. The appearance on storage after 7 days did not change appreciably. There was however, an evidence of decrease in consistency with rise in temperature from 10° to 45° as shown by fluid emulsion at 45° though at 10° the sample was equally gritty as the creams prepared in this laboratory. At 37° the cream was obviously less viscous by feel and at 45°, it was just a fluid emulsion but with no sign of creaming or separation.

2. Continuous Shear Rheometry

The rheograms of all the creams exhibited a plastic type of flow with yield value and thixotrophy within the range of temperatures studied indicating that all the materials were viscoelastic in nature. In a few materials, some characteristics types of spur-like protrussions and or bulges were observed (Appendixes I - VI). The apparent plastic viscosities and yield values in all formulations A to E generally showed that initial increase with rise in temperature up to a certain maximum value (T max) and decrease with rise in temperature therefrom. A 9% mixed emulsifier concentration samples data from A to E have been chosen in this work to give graphical presentations of various parameters with temperature variations. The remaining bulk date stands the same. The thixotropic break-down showed a linear decrease relationship with rise in temperature. All other parameters like the yield stress and apparent plastic viscosity increase with increased emulsifier concentration. The effect of concentration and temperature variations vary with the type of formulation as can be observed in Table III (1 - 6).

Generally, maximum consistency i.e. increase in plastic viscosity, yield value, and thixotropic break-down was observed at 20° but the yield values seemed to be optimum at 27° for all the formulations. The optimum apparent plastic viscosity, yield value and thixotropy also varied with the type of formulation.

FORMULATION A

i.e. CTAB 1 part and cetostearyl alcohol 11 parts • Refer to Table II -1

The rheograms showed characteristic type of bulges at all temperatures but were more evident at 10°. The bulges gradually changed to spur-like protrusions with increased mixed emulsifier concentration probably due to increase in complicity of the system. As the temperature increased, the rheograms became much simpler. The bulges, particularly at low temperatures were due to the reduction in shear stress even though the shear rate was increasing. This aspect of reduction of shear stress even with increasing shear rate was probably due to ejection of the material from the measuring gap

or perhaps due to slippage because of the material fracture. This observation is similar to that of Jefferies (1965) and to that made by Boylan (1967), using similar systems.

Results of 9% mixed emulsifier

Apparent - Plastic Viscosity Max. at 20°

= 1.72 Poise.

T(min) at 45° = 0.96 Poise.

Assuming a direct linear relationship between viscosity-temperature (Arrhenius Hypothesis). The viscosity-temperature coefficient will be

$$\frac{1.72 - 0.96}{25^{\circ}}$$

or 0.03 Poise/$^{\circ}$C.

The yield stress-temperature coefficient at

$27^{\circ} - 45^{\circ} = \frac{1127.73 - 957.28}{18}$

$= 9.47$ dynes/cm^2 per 1°C

Thixotropy - Temperature coefficient

$$\frac{69.0 - 20.7}{35} = 1.38 \text{ cm}^2/^{\circ}\text{C}$$

FORMULATION B

i.e. CTAB 1 part and cetostearyl alcohol 10 parts. Refer to Table III - 2.

The rheograms were similar to that of formulation A but with a little longer spur-like protrusion even at higher concentrations. In general the yield stress, apparent plastic viscosity and the thixotropic break-down, all have higher values at equivalent temperatures and concentrations than formulation A.

Results of 9% mixed emulsifier

Apparent plastic viscosity T(max) 20° = 1.49 Poise

T(min) 45° = 0.97 Poise

Viscosity-temperature coefficient = 0.021 Poise/$^{\circ}$C

Yield Stress-temperature coefficient

T_{max} 27° = 1183.0 dynes/cm^2

T_{min} 45° = 976.16 dynes/cm^2

Coefficient = 11.44 dynes/cm^3 per 1°C

Thixotropy-Temperature Coefficient

T(max) 10° = 66$\acute{6}$cm^2

T(min) 45° = 19.3 cm^2

Coefficient = 1.33 cm^2 per 1°C.

FORMULATION C

i.e. CTAB (1 part), cetostearyl alcohol (9 parts). Refer to Table III - 3

The rheograms were less complicated showing less bulging and simpler spur protrusions. The apparent viscosities, yield values and thixotropic effect are generally greater than in formulations A and B.

Result of a 9% mixed emulsifier

Apparent plastic viscosity T(max)
= 20° = 1.58 Poise

T(min) 45° = 0.88 Poise

Viscosity-temperature coefficient =
0.028 per $1^{\circ}C$

Yield stress - Temperature Coefficient

T(max) 27° = 1277.20 dynes/cm^2

T(min) 45° = 901.52 dynes/cm^2

Coefficient = 17.59 dynes/cm^2 per $1^{\circ}C$

Thixotropy-Temperature Coefficient

T(max) 10^{o} = 71.3 cm^2

T(min) 45^{o} = 17.0 cm^2

Coefficient = 1.55 cm^2 per $1^{o}C$.

That the increase in CTAB causes an increase in complicity and consistency was also observed by Talman *et al* (1968).

FORMULATION D

i.e. CTAB 1 part and cetostearyl alcohol 8 parts . Refer to Table III.4

The rheogram of this formulation was to some extent quite different from all the above in that there is no spur-like protrusions at all temperatures but characteristic bulges appear. There was relatively lower apparent plastic viscosities but increase yield values than all the above formulations at corresponding mixed emulsifier concentrations.

Results of 9% mixed emulsifier

Apparatus plastic viscosity T(max) 20^{o} = 1.40 Poise

T(min) 45^{o} = 0.92 "

Coefficient = 0.02 poise/$1^{o}C$

Yield stress-temperature

T(max) 27^{o} = 1275.1 dynes/cm^2

45^{o} = 905.9 "

Coefficient = 20.54 dyness/cm^2 per $1^{o}C$

Thixotropy - Temperature

T(max) 10^{o} = 74.3 cm^3

45^{o} = 21.0 cm^2

Coefficient = 1.52 $cm^2/1^{o}C$

FORMULATION E

i.e. CTAB 1 part and cetostearyl alcohol 7 parts, Refer to Table III - 5.

The shape of this rheogram is nearer to that of formulation D that is, has got a characteristic bulge but no spur-like protrusions. Generally in all respects it showed a lower consistency than all of the above formulations i.e. it has the lowest yield values, apparent plastic viscosities and thixotropy at equivalent mixed emulsifier concentrations.

Result of 9% mixed emulsifier

Apparent plastic viscosity T(max) 20^{o} = 1.30 poise

T(min) 45^{o} = 1.01 "

Viscosity-temperature-coefficient

= 0.011 poise per 1°C

Yield stress-temperature relationship

= T(max) 27° = 1386.2 dynes/cm^2

T(min) 45° = 920.83 "

Coefficient = 25.85 dynes/cm^2/1°C

Thixotropy-temperature

T(max) 10° = 64.3 cm^2

T(min) 45° = 22.3 cm^2

Coefficient = 1.20 cm^2/1°C

Commercial Clotrimazole Cream

The rheograms were similar to those prepared in this laboratory i.e. they are of plastic type of flow with yield values and thixotropy. The main difference is the large spur-protrusion at 10° but with rheogram becoming much simpler as the temperature increased. At 45°, the rheogram was to a greater or lesser extent of Newtonian flow.

Result of clotrimazole cream

Apparent plastic viscosity

T(max) 20° = 1.65 poise

T(min) 45° = 0.09 "

Coefficient = 0.06 poise per 1°C

Yield stress-temperature relation

T(max) 20° = 2056.2 dyness/cm^2

T(min) 45° = 73.40 "

Coefficient = 79.67 dyness/cm^2 per $1^{\circ}C$

Thixotropy -temperature relation

T(max) 10° = 69.7 cm^2

T(min) 45° = 0.0 cm^2

Coefficient = 1.99 $cm^2/1^{\circ}C$

Table III - 1: FORMULATION A 1 part Surfactant : 1| parts Alcohol

Shear stress (dyness/cm^2)

Mixed Emulsifier Conc.	10°	20°	27°	37°	45°
7	1704.5	3037.3	2950.3	2581.5	1816.7
8	2872.5	3783.5	3510.3	2872.5	1891.8
9	3070.06	4056.7	3745.4	3264.5	2690.8
10	3469.4	4138.7	4097.7	3496.7	2800.1
11	4807.97	4985.5	4657.7	3928.9	2806.0

Yield Stress (dynes/cm^2)

Mixed Emulsifier Conc.	10°	20°	27°	37°	45°
7	425.1	773.4	897.3	895.4	625.8
8	672.3	890.1	1077.6	997.2	633.6
9	713.9	947.4	1127.7	1117.4	957.3
10	725.5	1187.9	1480.7	1307.7	1068.7
11	1285.93	1414.6	1784.3	1460.5	

Apparent Plastic Viscosity (Poise)

Mixed Emulsifier Conc.	10°	20°	27°	37°	45°
7	1.19	1.27	1.14	0.93	0.66
8	1.21	1.60	1.35	1.04	0.70
9	1.30	1.72	1.40	1.13	0.96
10	1.52	1.63	1.44	1.21	0.96
11	1.95	1.98	1.59	1.26	—

Thixotropy (cm^2)

Mixed Emulsifier Conc.	10°	20°	27°	37°	45°
7	49.6	41.0	32.0	16.3	10.6
8	64.0		33.7	18.0	15.0
9	69.0	50.3	45.7	22.0	20.7
10	77.7	52.3	41.3	31.3	21.3
11	108.5	64.0	44.1	36.0	30.0

Results of various rheological properties of formulation A Concentrations are in %w/w.

Table III - 2 FORMULATION B 1 part Surfactant: 10 parts Alcohol

Shear stress (dynes/cm^2)

Mixed Emulsifier Conc.	10°	20°	27°	37°	45°
7	2294.7	3345.1	3167.4	2622.5	1844.0
8	2335.7	3459.8	3387.4	2872.5	1912.3
9	2485.9	3834.1	3735.7	3196.2	2731.8
10	3182.6	4138.7	4070.4	3619.6	3032.0
11	3428.4	4808.6	4480.5	3892.8	3387.4

Yield Stress (dynes/cm^2)

Mixed Emulsifier Conc.	10°	20°	27°	37°	45°
7	596.7	890.0	940.5	884.8	564.1
8	603.5	947.9	1108.8	1055.4	373.6
9	651.2	1133.8	1183.0	1079.2	976.2
10	1067.9	1165.1	1476.7	1329.0	108.4
11	1047.6	1333.5	1534.5	1482.8	1125.3

Apparent Plastic Viscosity(Poise)

Mixed Emulsifier Conc.	10°	20°	27°	37°	45°
7	0.93	1.36	1.23	0.96	0.76
8	0.96	1.39	1.26	1.61	0.74
9	1.02	1.49	1.41	1.17	0.97
10	1.17	1.62	1.44	1.27	1.07
11	1.32	1.92	1.63	1.33	1.25

Thixotropy (cm^2)

Mixed Emulsifier Conc.	10°	20°	27°	37°	45°
7	50.0	41.7	37.3	19.0	10.7
8	58.7	48.7	41.6	26.6	16.7
9	66.6	50.0	45.7	30.7	19.3
10	92.0	69.3	57.7	42.7	24.6
11	102.0	69.7	63.7	43.3	26.3

Results of various rheological properties of formulation B. Concentrations are in %w/w.

Table III - 3 FORMULATION C 1 part Surfactant: 9 parts Alcohol

Shear Stress (dynes/cm^2)

Mixed Emulgent Conc.	10°	20°	27°	37°	45°
7	2731.8	2841.0	2882.1	2540.6	1960.9
8	2867.2	3145.7	3144.8	2768.6	2062.5
9	3319.1	3869.6	3920.1	3360.1	2499.6
10	3508.9	4633.5	3974.8	3551.3	2883.0
11	4261.6	5081.2	4971.9	4357.2	3305.5

Yield Stress (dynes/cm^2)

Mixed Emulgent Conc.	10°	20°	27°	37°	45
7	487.8	724.1	875.7	873.3	611.3
8	674.7	848.5	1062.7	943.2	717.4
9	735.6	1014.8	1227.2	1200.0	910.5
10	829.1	1126.4	1386.1	1327.4	1075.1
11	1086.6	1333.3	1919.0	1716.4	1178.3

Apparent Plastic Viscosity(Poise)

Mixed Emulgent Conc.	10°	20°	27°	37°	45°
7	1.00	1.26	1.11	0.92	0.75
8	1.21	1.27	1.16	0.98	0.77
9	1.43	1.58	1.49	1.20	0.88
10	1.48	1.61	1.43	1.23	1.00
11	1.76	2.07	1.69	1.40	1.18

Thixotropy (cm^2)

Mixed Emulgent Conc.	10°	20°	27°	37°	45°
7	54.0	45.7	42.3	31.6	13.7
8	63.0	49.6	45.7	33.0	14.6
9	71.3	57.6	53.0	-	17.0
10	75.7	67.6	54.7	34.0	21.3
11	94.7	68.3	56.0	38.5	23.5

Results of various rheological properties of formulation C. Concentrations are in %w/w.

Table III - 4 FORMULATION D 1 part Surfactand: 8 parts Alcohol

Shear Stress (dynes/cm^2)

Mixed Emulgent Conc.	10°	20°	27°	37°	45°
7	2431.3	1663.6	2648.9	2478.3	1953.2
8	2731.8	2913.5	2995.4	2722.7	2308.4
9	3373.7	3459.8	3674.3	2882.1	2561.9
10	3657.9	3715.3	3770.0	3510.4	2991.3
11	3879.2	4288.9	4384.5	3797.2	3660.6

Yield Stress (dynes/cm^2)

Mixed Emulgent Conc.	10°	20°	27°	37°	45°
7	716.8	682.4	799.1	958.8	591.5
8	771.8	800.7	1063.0	1141.6	823.2
9	791.6	929.1	1275.1	1179.8	905.9
10	738.6	1020.8	1323.1	1328.8	1095.5
11	1050.4	1159.6	1673.3	1485.8	1459.0

Apparent Plastic Viscosity (Poise)

Mixed Emulgent Conc.	10°	20°	27°	37°	45°
7	0.95	1.10	1.03	0.83	0.75
8	1.08	1.17	1.07	0.87	0.82
9	1.43	1.40	1.33	0.94	0.92
10	1.61	1.49	1.35	1.21	1.05
11	1.57	1.73	1.50	1.28	1.22

Thixotropy (cm^2)

Mixed Emulgent Conc.	10°	20°	27°	37°	45°
7	50.0	47.3	40.0	30.7	16.0
8	57.7	49.7	46.3	33.0	18.6
9	74.3	55.3	54.3	33	21.0
10	80.3	64.0	56.3	40.0	23.3
11	88.5	66.3	57.7	41.7	26.3

Results of various rheological properties of formulation D.
Concentrations are in %w/w.

Table III - 5 FORMULATION E 1 part Surfactant : 7 parts Alcohol

Shear Stress (dynes/cm^2)

Mixed Emulsifier Conc.	10°	20°	27°	37°	45°
7	2007.9	2950.3	2018.6	2212.8	2035.2
8	2800.1	3071.5	3032.3	2618.4	2389.4
9	3208.6	3186.7	3258.9	2868.3	2472.3
10	3336.9	3369.9	3783.5	3633.3	2477.6
11	3797.2	4302.6	4384.0	3701.6	3619.6

Yield Stress (dynes/cm^2)

Mixed Emulsifier Conc.	10°	20°	27°	37°	45°
7	392.3	632.4	750.0	803.1	666.9
8	615.6	753.6	934.1	940.2	902.3
9	699.8	825.0	1386.2	1140.4	920.8
10	544.7	1097.4	1397.5	1500.0	1047.3
11	732.3	1308.9	1808.3	1507.8	1433.4

Apperent Plastic Viscosity (Poise)

Mixed Emulsifier Conc.	10°	20°	27°	37°	45°
7	0.89	1.28	1.28	0.78	0.75
8	1.21	1.25	1.26	0.93	0.82
9	1.38	1.30	1.03	1.18	1.01
10	1.55	1.48	1.34	1.18	1.01
11	1.10	1.66	1.42	1.21	1.20

Thixotropy (cm^2)

Mixed Emulsifier Conc.	10°	20°	27°	37°	45°
7	42.3	40.7	31.6	18.5	19.0
8	61.7	49.7	42.7	27.7	21.5
9	64.3	50.0	44.3	31.3	22.3
10	78.3	63.7	55.3	38.7	23.3
11	91.5	66.7	59.7	41.3	27.0

Results of various rheological properties of formulation E. Concentrations are in %w/w.

TABLE III - VI CANESTEN CREAM

Results of various rheological properties of Canesten Cream. Concentrations are in %w/w.

Canesten Cream	Average Readings				
	10^0	20^0	27^0	37^0	45^0
Shear Stress (dynes/cm^2)	4439.2	5040.2	3873.2	1392.2	236.8
Yield Stress (dynes/cm^2)	1778.4	2056.2	1514.7	446.7	73.40
Apparent Plastic Viscosity (Poise)	1.47	1.65	1.31	0.52	0.09
Thixotropy (cm^2)	69.7	44.0	35.7	11.0	NIL

NOTE* The Rheograms of a 9% emulsifier emulsions and 'Canesten Cream' obtained from various formulations at different temperatures are attached as at appendix I-VI at the back page.

CHAPTER 4

DISCUSSION

1. Continuous Shear Rheometry and Low Temperature

Results at 10°C temperature were inconsistent. This could be attributed to many factors like the physico-chemical properties of the ingredients as pointed out in Chapter One. Davis (1969 a, b) in the study of the viscoelastic properties of some pharmaceutical semi-solids, ointments and creams, pointed out that the apparent viscosity could not be determined accurately at low temperature as the test samples were ejected from cone-plate gap. He attributed this possible elastic recovery or fracture of the material or both. Barry and Grace (1972) also observed similar effects. They also observed a drastic decrease in shear stress immediately after the maximum shear stress ("Static Yield Value") has been attained even though the shear rate was still on the increase. At times visible ejection of the test material was observed in this laboratory during the testing of Samples. Material was seen

climbing the sides of the cone. All these irregularities seriously cause the errors in the visco-elasticity determinations. Lenk (1978) and Wood et al (1964) explained that the expulsion of material from the measuring gap may not be a function of the viscosity alone but also due to fracture of the adhesive forces between the samples and the viscometer leading to slippage. They therefore postulated that measurement at lower shear rate might reduce this effect of flow inhomogeneity to a great extent because essentially flow inhomogeneity was caused by the presence of two or more phases which mutually interact such as to produce local perturbations in the stream lines. Again this might be due to interfacial forces, hydrogen bonding or other molecular interaction or a tendency on the part of the disperse phase to crystallise so as to increase its volume fraction at the expense of the continuous phase.

At low temperature sample material was observed to have dried out an effect termed 'thermal drying out' by Barry and Saunders (1971 b) and they attributed this to the possibility of the disperse phase to cristallise.

However, from all indications, it could be seen from the results that the consistency decreased with lowering of temperature from 20^{o} to 10^{o} in all

the formulations including the canesten cream commercial sample. This is particularly more evident when looking at the yield stress values which showed an obvious decrease with lowering temperatures from 27^{o} to 10^{o}. This perhaps contradicts the popular concept that for optimum rheological stability of creams and ointment, storage should be done at temperatures below 20^{o} because in general, all the rheological properties of at least the creams tested here are higher (more stable) at 20^{o} or 27^{o} than at 10^{o}.

Table IV - 1: Viscosity, Yield Stress and Thixotropic-Temperature Coefficient of a 9% Mixed Emulsifier Emulsion

Surfactant/ Alcohol Ratio	Viscosity Temperature coefficient at T_{max} 20^{o} - 45^{o} (poise/^{o}C)	Yield Stress-Temperature coefficient at 27^{o} - 45^{o}C per ^{o}C	Thixotropic-Temperature coefficient at 10^{o}-45^{o} ($cm^{2}/^{o}C$)
A	0.030	9.47	1.38
B	0.021	11.49	1.33
C	0.028	17.59	1.55
D	0.019	20.54	1.52
E	0.018	25.85	1.20
Commercial Sample	0.062	80.07	1.99

2. The Shear Stress

The Shear Stess is the viscous drag of a fluid when in laminar flow and is read directly from the instrument reading multiplied by the cone shear stress constant. The shear stress usually gives a direct reflection of the viscosity of a Newtonian fluid but does not tell much in case of non-Newtonian fluids like those that are being investigated here since it does not indicate anything about the yield stress or the thixotropic break-down although the later is also computed directly from the rheogram. As has been mentioned, the yield value is an amount of initial shear stress that must be applied before a fluid starts to flow. Above this point, the shear rate becomes directly proportional to the shear stress.

The shear stresses indicated in the results in tables I, II, 1-6 are not necessarily the maximum shear stresses attained but are only indicative of the shear stress at the apex of the shear rate (100 r.p.m.) Ideally, the shear stress should be maximum at the maxium shear rate but in practice sometimes it is not but lower than the maximum. This is due partly because the shear rate of maximum stability that can be measured has been exceeded or that because the shear rate is too

great, part of the test material in the measuring gap has been ejected as was seen climbing the sides of the cone.

Although the shear stress does not directly give the viscosity of a non-Newtonian fluid, it however, generally gives a rough guide to the viscosity. This is so particularly for a less viscous fluid. From the results in table III(1 - 6) it could be seen that the shear stress generally increases with increase in mixed emulsifier concentration thus the principle of 'self-bodying action' termed by Barry (1975) has been elucidated. The shear stress also shows maximum at a particular temperature for any given formulation which indicates that the shear stress maxima is a factor not only of the mixed emulsifier concentration but also of the surfactant/alcohol ratio and the temperature. It becomes maximum at 20^{o} for formulations A and B, at 20^{o} - 27^{o} for formulation C and generally at 27^{o} for formulation D and cleary at 27^{o} for formulation E. The maxima is generally higher in formulations A, B and C than in D and E for any one given concentration. Similarly, a shear stress maxima was shown at 20^{o} for the commercial sample of Clotrimazole cream.

3. The Yield Stress(value)

The yield value referred to here is the conventional yield value (in contrast to the minimum or maximum (static) yield values). The conventional yield value is the intercept of the linear portion of the down curve of a rheogram at zero shear rate and usually defined as the minimum tangential shearing force necessary to cause flow i.e. the energy-input necessary to maintain a constant ratio of shear rate to shear stress in a system whose structure has been destroyed totally or in part by previous shear (in the cause of determining the up curve of the rheogram). The yield stress also indicate the degree to which the internal structure of a system has been destroyed by a given shear (Levy 1962). At some point (spur point) a further increase in shear stress and/or duration cause no further increase in the yield value, namely when all the weak secondary bonds between particles have been broken and the dispersed units consist solely of primary particles, Lenk (1978).

From the results of these investigations, it could be seen that the yield values increase with increased emulsifier concentration. With regard to temperature effect, like the shear stress, it becomes

optimum at certain temperature specific for a particular formulation and decrease with further increase or decrease in temperature. In formulations D and E, the optimum yield value was generally recorded at 37°. This increase in the yield value signifies that a greater energy input is necessary to prevent structure reformation. The difference in the optimum temperatures between formulations A, B, C, D and E clearly demonstrate the possibilities of selective modification of yield values by simply modifying the surfactant/alcohol ratio. With regard to topical emulsions which need to be stored and transported, formulations A, B and C will be preferred so that as soon as it is applied, the yield value is then decreased and easy spread since ease of application of a pharmaceutical semi-solid or cosmetic cream to the surface of the skin is an important factor in consumer's acceptance. Secondly, it could also be seen that the yield value was decreased between 27° to 37°. This pattern followed the same norms as the shear stress.

4. The Apparent Plastic Viscosity

The apparent plastic viscosity indicates the degree of 'softness' when the material is rubbed at certain shear rate. It is also an indication of the physical stability of emulsion. Each individual applies cream to the skin with slightly different motion, stroke and rate. An approximate rate of shear was encountered when spreading a cream or ointment on a surface on assuming a stroke average of 6 cm, a rate of 4 strokes/sec, and cream layer of 1 - 3mm. Under these conditions, a shear rate of 120 sec^{-1} was calculated, Boylan (1966). If this value is used as a guide, recognizing its short comings, an estimate of the spreading resistance can be graphically shown by extending a dashed line through the rheogram of 120 sec^{-1} which occurs in a region of great resistance to flow. In nearly all the rheograms, the area between 0 - 250 sec^{-1} appear to be an extremely important one when characterizing the spreading properties of pharmaceutical semi-solids. When all other variables (yield values, thixotropy etc.) are held constant, an increase in viscosity generally minimizes creaming or sedimentation and therefore greater consistency.

The results here indicate that the apparent viscosity increases with increase in mixed emulsifier concentration at all temperatures and in all formulations at least within the range studied in this laboratory i.e. 7 - 11% concentrations. It has already been indicated that the measurements of viscosity cannot be determined accurately below 20°. It can however be safely stated that the apparent plastic viscosity decreases with rise in temperature from 20° to 45° in all formulations as well as the commercial sample of Clotrimazole cream. The surfactant/alcohol ratio seemed to have an indirect effect on the apparent plastic viscosity within the range of ratios considered here but certainly it seemed to be optimum at formulation C i.e. surfactant/alcohol ratio 1:9 (taking an example of a 9% and 11% concentration at 27° in Table III 1 to 5).

5. Thixotropy

Thixotropy defined as the time dependent reversible sol-gel behaviour otherwise known as an isothermal and comparatively slow recovery on standing of a material of a consistency lost through thinning. At rest, the material becomes rigid

resembling a gel. As shear is applied, flow starts, the structure begins to break i.e. gel-sol transformation. The applications of thixotropy in formulations has already been outlined in Chapter One.

The results of thixotropy as obtained here are much more reliable in that they showed a definite increase with increase in mixed emulsifier concentration and a direct decrease with increase in temperature, Boylan (1966), Talman and Rowman (1968) and Barry (1975) all reported a linear decrease in thixotropy with rise in temperature in cream emulsions. The pattern is the same in all formulations and the clotrimazole commercial sample. Not much difference can be detected merely by altering the surfactant/alcohol ratio. This was probably because in all the formulations the surfactant component has far exceeded its critical micelles concentrations and that any further increase has little or no effect on thixotropy, Van Wazer (1963) so that any further gel-like network formed depends entirely on the total concentration of the 'structured' vehicles added (mixed emulsifier).

6. Formulation Consideration

The fact that most pharmaceutical cream emulsions exhibit non-Newtonian flow behaviour and many of them time-dependent with yield values; it is important that the desired emulsion consistency that will provide the desired stability (high viscosity) and yet the appropriate flow characterstics that must be attained should be aimed at. It has already been mentioned that the viscosity of an emulsion could be altered by simple manipulations of the composition of the oil and water phases. It is also generally known that when all other variables are held constant, an increase in viscosity minimizes creaming or sedimentation and since emulsion should also flow or spread and that since higher viscosity favours stability, thixotropy in an emulsion is desirable. The presence of a yield value is also some assurance of reasonable stability by preventing the creaming or semimentation processes since there is no flow below the yield stresses, the apparent viscosity at low shear then becomes infinite. When it is desired to pour some of the emulsion cream from its containter, it is

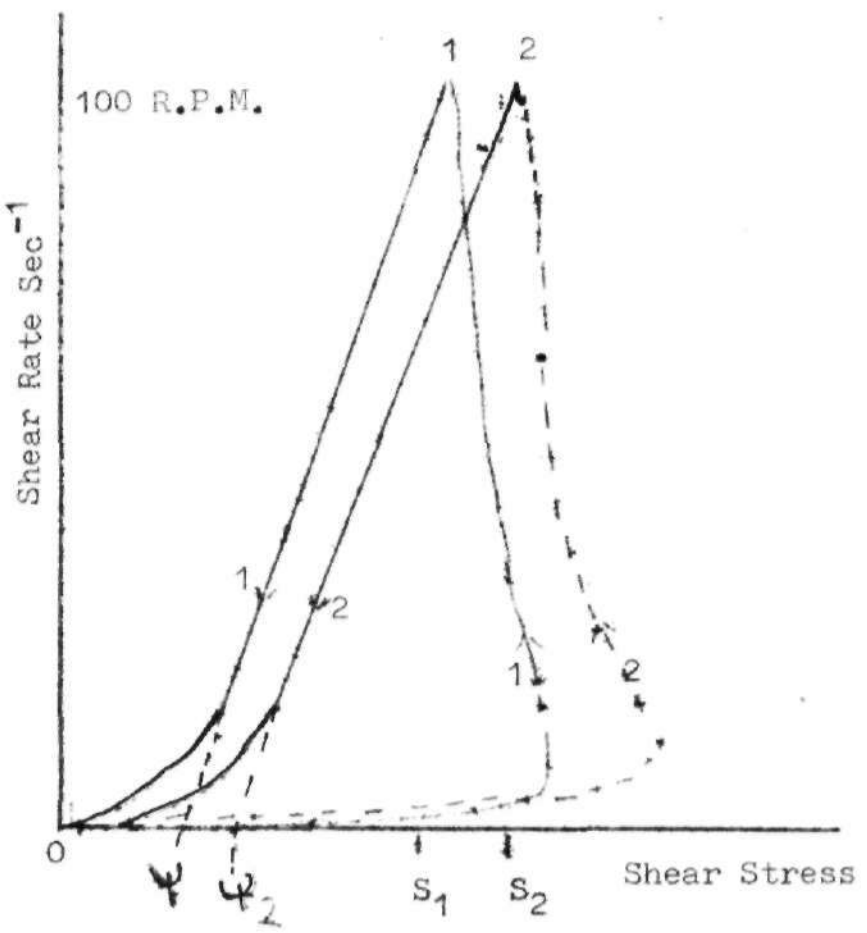
shaken or sheared well, at shear stress considerably above the yield value. The agitation breaks down temporarily the thixotropic structure such as the 'house-of-cards', reducing the yield value to zero and lowering the apparent viscosity. This makes it easy for pouring. Back on the shelf, the viscosity slowly increases again and the yield value is restored as Brownian motion rebuilds the 'house-of-cards'. The optimum flow curve therefore has to be a compromise of at least the three for a particular formulation and purpose of the cream.

As could also be seen from table IV - 1, most of the cream bases show only a little difference in temperature coefficients of plastic viscosity, thixotropy and yield value. If it is desired that it is the viscosity that will be optimized, formula E provides the least temperature sensitive product in contrast to formula A. The temperature-yield value coefficient showed a reverse order and the thixotropy-temp. relation has its optimum in between both ways and therefore formula C (surfactant/alcohol ratio 1:9) will be preferred. This observation is in absolute agreement with the surfactant/alcohol ratio of 1:9 in the British Pharmacopoeia, 1980.

7. The Self-bodying Action of Mixed Emulsifier and Gel-network Formation

The mechanism whereby mixed emulsifiers of the surfactant/long chain alcohol are able to form mobile emulsion when present in low concentrations (1 - 5%) and semi-solid emulsions when present in moderate concentrations or their ability to stabilize and control consistencies by altering the concentration of mixed emulsifier within wide limit is referred to as the 'self-bodying' action. Schalman and Cockbain (1946) were the first to describe this phenomena and has since found a wide appreciation both in pharmaceutical and cosmetic industries. The work of Barry (1968), Barry and Sanders (1970 a, 1971 a, 1971 b) and Becher (1965) are good examples. Combinations of anionic, cationic or non-ionic surfactants with fatty acids or alcohols are widely used to control the rheological behaviour of emulsions by varying the concentration of mixed emusifier (see figure 4..1 for a typical rheogram). An essential feature of this action is that a significant elastic component is introduced into the rheological behaviour which distinguishes such emulsions from preparations made with simple emulsifiers, Sherman (1964), Beacher (1965) and

Figure 4 -1: Effect of mixed emulsifier concentration at 20° (1) 9% (2) 10%



Compare rheograms 1 and 2 of mixed emulsifier at 20° for formulation C

Ψ = 1014.8 dynes/cm^2

Ψ_2 = 1126.4 dynes/cm^2

S_1 = 3869.6 dynes/cm^2

S_2 = 4033.5 dynes/cm^2

Thixotropy 1 = 57.0 cm^2

2 = 67.6 cm^2

Martin et al (1964). According to Barry (1969), in the usual concentrations of the surfactants employed (5 - 10%), the concentrations used are greater than those necessarily required to provide a complex, condensed monomolecular film at the interface. Also Ekwall et al (1969), Mulley (1964) and Gbefwi (1978) have claimed the same. The excess surfactant remains in the aqueous phase either monodisperse or as miscelles depending on its c.m.c. and the temperature and this is what modifies the rheological properties of the emulsion. Below the c.m.c., only mobile somewhat unstable emulsions are formed, above the c.m.c., micelles pseudophase is present. The formation of a complex mixed monomolecular film at the oil/water interface though important, but is however not a prerequisite for good stability since dilute monolayers of sodium oleate with oleic acid have been shown to be effective, Pickett (1975).

The self-bodying action has evidently been shown from our results in that all rheological parameters at our disposal i.e. the apparent plastic viscosity, the yield value and the thixotropic effect increase progressively with increase in mixed emulsifier concentration owing to increase in the amount of gel network structure present. These

results are very much in agreement with those obtained by many authors using similar types of mixed emulsifiers, Sherman (1965), Barry (1968), Barry and Saunders (1971 a, b, c) Barry and Eccleston (1973), Davis (1969) and Talman and Rowan (1970 a,b,c). The progressive increase in consistency was said to be due to the formation of stronger gel network. Although low mixed emusifier concentrations of around 1 - 5% mixed emulsifier were not tried here, it has however been shown by Mulley (1964), Barry (1975) and Talman and Rowan (1970 a, b) that the gel networks formed from low concentrations of mixed emulsifiers are not so extensive and are easily irreversibly disrupted i.e. low thixotropic break down and almost Newtonian behaviour. Works on creep and oscillatory properties on such emulsions, Davis (1969, 1971), Sherman (1970) and Warburton and Davis (1969) all show similar evidence.

For ionic surfactants in mixed emulsifiers, some additional explainations have been put forward to show why they are generally more effective at equimolar concentrations than non-ionics such as hindrance and electrostatic repulsion. The consistency of any emulsion also, however, depends largely on the rate of cooling of the emulsion during manufacture (see figure 4.2), Boylan et al (1962),

Barry (1975) and Schott (1975), and the mechanical dispersion process since this affects the degree of partitioning of the oil-soluble component before the structures are 'frozen' in position. Structure build up is rapid with ionics as was pointed out in Chapter Three and occurs during the cooling process whereas structural changes occur over a period of several hours, weeks or months in cooled non-ionics, Barry and Saunders (1971 c). This offers an advantage for laboratory investigations because one is more concerned with the properties of an emulsions after it has come to equilibrium. It has been clearly pointed out in the literatures, Boylan et al (1962) that low temperature interaction is very important if not more important in non-ionics and that equilibrium takes much longer time to come by. It could as well be possible that ionic surfactants behave rather differently from non-ionics. This, however, should by no means serve as a criteria for choice of the type of emulsifier. Primarily, the type of emulsion that is to be prepared determined the type of emulsifier to be used i.e. either a water-in-oil or oil-in-water emulsion. As a general consideration; a particular class or combinations of emulsifiers is selected primarily on the bases of:

i) the potential toxicity when ingested, injected or spread on the skin

ii) chemical incompatibilities

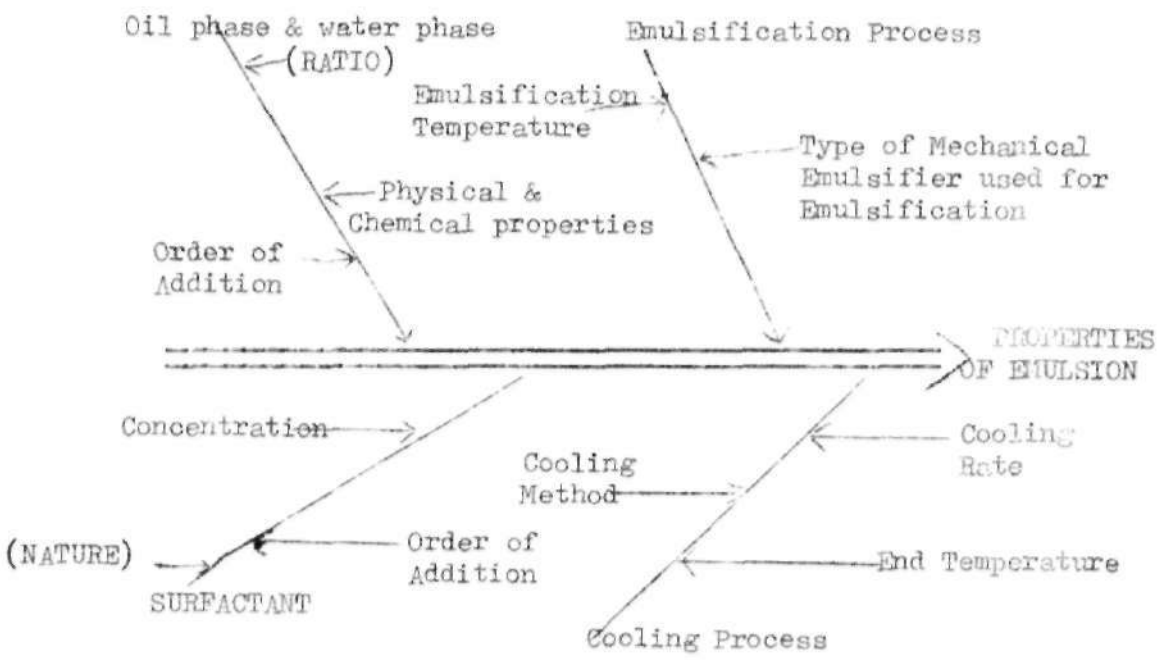
iii) the cost of emulsifiers

iv) the type of emulsion desired

v) the 'shelf-life' stability required.

However, on the basis of experience, one should be able to prejudge problems of toxicity, cost and major incompatibilities, and thus the major problem associated with choice of an emulsifying system narrows

Figure 4 - 2 Cause and Effect Diagram for the factors affecting the properties of emulsions (Mitsui, T, Tahara, S and Machida, Y. 1966).



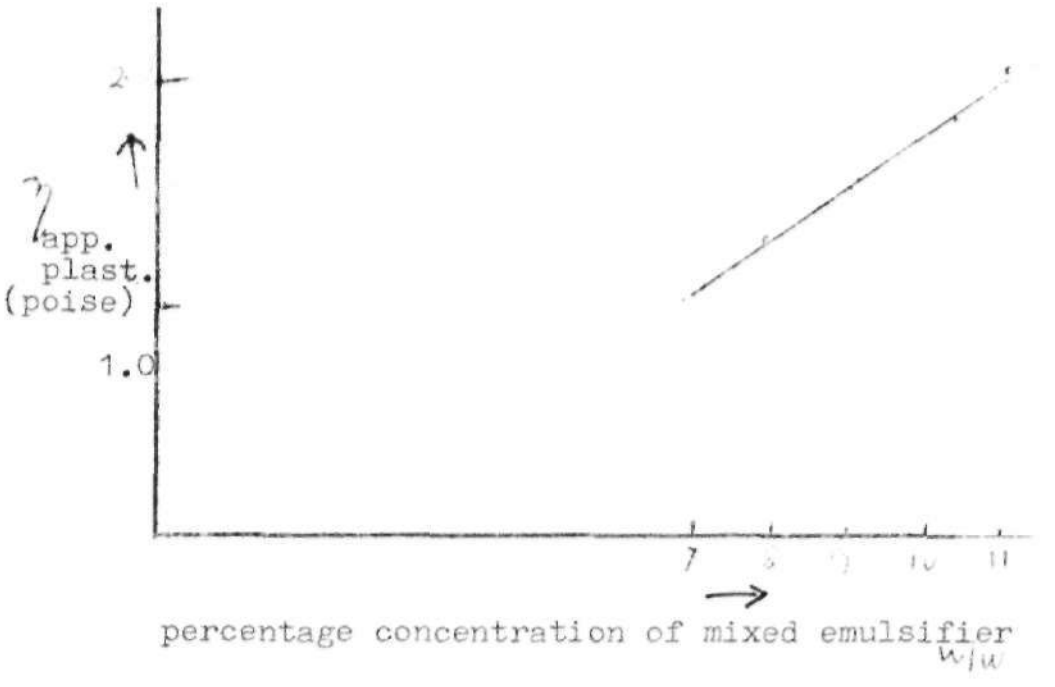
down to finding the system giving the desired type of emulsion, as well as the optimum elegance, consistency and physical stability. Ionic surfactants offer additional advantages as will be outlined later in addition to preservative effect of cationics though prone to toxicity problem when in large dose.

As has been seen from these results using the cationic surfactant with a fatty alcohol, equilibrium was easily reached within few hours in contrast to non-ionics which may take weeks or even months. Also the ionic character of CTAB for example, has been shown to create an electrical double layer at the oil-water interface thereby adding an electrostatic repulsion factor in addition to the complex-condensed liquid film barrier (not solid as was explicitly assumed) which reduces effective particle-particle collusions and inhibits coalescence, Higuchi et al (1962) and Rowe (1965).

In conclusion, it is considered that the method of aggregation of micelles as monomolecular layer at the o/w interface is more important than the theory of polymolecular adsorption of the structure suggested by Cockbain (1946) or the electrical theory of Higuchi et al (1962).

8. Effect of Mixed Emulsifier Concentration

The ability to produce stable emulsions of any desired consistency by merely altering the concentration of mixed emulsifier is valuable in formulation work. The 'self-bodying action' of such emulsifiers has already been discussed in section 4 .7. In the results obtained in this work, the emulsion consistencies increase with increase in emulsifier concentrations as the gel-network forms further in the continuous phase. In a continuous shear plot of viscosity verses concentration a gradual increase from 7 - 11% in all formulations will be a graph as under:



Barry (1968) and Barry and Saunders (1970 b) obtained similar result using cationic surfactant (cetrimide) with cetostearyl alcohol in a ratio 1:9 for concentration 6 - 10% and a steeper increase from 10 - 16%. Similar results were also obtained in creep experiments by Barry and Eccleston (1973 a). In such experiments for low mixed emulsifier concentrations i.e. fluid emulsions, the limit of viscoelastic linearity will be low and the data scattered and this shows the idea that the network formed from low concentrations of mixed emulsifier are not extensive enough and are therefore easy irreversibly disrupted. Similar data will be expected even for higher concentrations of mixed emulsifier when the experiment is conducted at a much elevated temperatures. There is usually a minimum amount of emulsifier necessary for stability which must be above the C.M.C. of the surfactant just sufficient enough to form a condensed liquid monomolecular film at the oil/water interface. Although the concentration of mixed emulsifiers normally employed in making the emulsion is in every case much greater than that required to form a condensed monomolecular film, the excess material is important when considering the stability of the

emulsion. It could therefore be concluded that interfacial rheology is not the dominant factor for determining consistency, nor is the variable in particle size or particle size distribution. The rheological behaviour of these emulsions depend on the formation of viscoelastic gel-network in the continuous phase and the nature and properties of these networks control emulsion behaviour.

It may however, be assumed safely that the increase in consistency that stabilizes more oil/water interfacial area as the emulsifier increases above the c.m.c. was due to increase in absorption of the emulsifier ions. The problem is whether the additional emulsifier is adsorbed as single ions forming close-packed monolayer or aggregated or micellar groupings. Miceller adsorption has been proposed especially at the solid-liquid interface, Fuertenan (1956). On the other hand, the generally recognised physical model of a condensed mixed monolayer with the hydrophobic portion of surfactant at the oil/water interface and the hydrophilic portion sticking outward into the water phase (Gbefwi, 1978) would be seen to be preferred if there are additional single molecules available. Another proposal put forward by Barry (1975) for the increase in consistency with rise in emulsifier

concentration was said to be due to increased diffusion of alcohol from the hot dispersed phase into the contin ous phase, where it forms a visoelastic network on cooling. Once the emulsion globules are well linked together by a gel structure of sufficient size, further addition of this network may have a relatively minor effect on the viscoelastic parameters. This is probably due to the fact that stability limit of the surfactant has been exceeded. Official B.P. and B.P.C. o/w creams have concentrations of surfactant above their c.m.c. values and these preparations show evidence of structure in continuous phases as was confirmed by Davis (1969).

9. The Effect of Alcohol/Surfactant Ratio

In considering the ability of a mixed emulsifier to form a semi-solid emulsion i.e. the theory of 'self-bodying' action, the part played by the surfactant and the alcohol needs examination. According to the findings of Axon (1956), Barry and Shotton (1967 a, b), and Talman et al (1967, 1968), the surfactant component should be capable of combining with the amphiphile to form a complex, condensed and closely-packed film at the oil/water interface to stabilise the emulsion.

It should also be present in a sufficient amount to form micelles in the continuous phase, Barry (1969). As already pointed out, in the usual concentrations of surfactants used in emulsions, the concentration is usually considerably above the c.m.c. at a particular temperature, Barry (1968 a), and that considerable order exist in the emulsion in a form of gel-network from the excess amount. The continuous shear experiment disrupts this entrapped continuous phase and some of the solubilised dispersed phase. The extent of gel-network was found to be related to this thixotropic break-down and the hysteresis loop area and the increase in plastic viscosity, Barry (1968 a).

Our results showed that the thixotropic break-down, the apparent plastic viscosity increase with increase in surfactant concentration to a maxima. This maxima depends on the alcohol part, that is to say, on the appropriate surfactant-alcohol ratio, the thixotropy increased with increase in mixed emulsifier concentration. An optimum of 1:9 or 1:10 was found from these results. This however, does not support the theory of self-bodying action but is in agreement with the findings of Talman et al (1968 a, b) when using ionic:

surfactants cetrimide and sodium lauryl sulphate and some non-ionics with Ferrenti-Shirley apparatus who examined the rheological effect of some liquid paraffin emulsions found a maxima in consistency with increase in surfactant concentration at ratio of alcohol/ surfactant 9:1 for ionics. Both results (Barry 1969, Talman et al 1968 a) were therefore not in agreement with that of Axon (1956) who reported an exponential increase of both yield values and the plastic viscosities with increase in surfactant concentration in an autoclaved liquid paraffin emulsion containing anionic sodium lauryl sulphate surfactant and a fixed concentration of cetyl alcohol. These discrepancies were said to be attributed to the method of measurement by Barry (1969) since the continuous shear experiment does not measure materials in their rheological ground state. Barry therefore accordingly concluded his own by saying that provided the surfactant concentration is not so high, as to promote instability, the consistency of the system increases as the concentration of alcohol increases in the oil phase at the temperature such that an amount will diffuse out from the oil phase into the aqueous phase. More will diffuse out as the concentration in the oil phase increases due simply to a raised concentration gradient from the oil to water to form a semi-solid emulsion. However, the amount of alcohol that

diffuses into non-micella phase is small. When sufficient surfactant is available, large quantity of the alcohol may be solubilised within the micelle alongside the surfactant molecules. The findings of Talman et al (1967) using various types of alcohols oleyl, lauryl and cetosteryl which showed that only fluid emulsions were produced with oil-soluble component whose concentration is below the saturation point in the oil phase and these emulsions produced only low apparent viscosity and zero static yield values even with increase of the oil soluble component but not above the saturaion point in the oil support this evidence and that for a semi-solid to be formed, a water soluble component must be present. The relationship between viscosity and surfactant concentration was however, not an easy phenomena as was also accepted by Sherman (1959 and 1963). In the findings here, no such categorical statement can be made, but only to support Barry's postulates above. Two things are certainly clear, firstly that these rheological parameters depend to some extent on the alcohol/surfactant ratio and not entirely on the concentration of either of them and secondly the ratios 8:1, 7:1 are rheologically less

stable for cetostearyl alcohol and (CTAB) as mixed emulsifiers. The yield value also increases as the ratio of surfactant part increases from ration 11:1 up to ratio of 7:1 (see table IV - 1).

As for the oil-soluble component in a mixed emulsifier, Barry & co-workers postulated that for such an amphiphile to be effective, it should by itself promote w/o emulsions and be capable of complexing with hydrophilic component to form a closed-packed complex film at the o/w interface. The melting point of such an amphiphile should be sufficiently high so as to precipitate solubilised materials at moderate temperature of 25 - 27°. It should also be present in at least sufficient concentration to form the mixed monolayer film when mobile emulsion will be formed but should be near or above its saturation concentration enough above its solubility in the oil phase so that some will diffuse out of the oil phase to precipitate on cooling to form semi-solid emulsions. Barry (1968) also found a linear increase in plastic viscosity

and yield value for cetostearyl alcohol above their saturation concentration in the oil phase. All these findings are in agreement with the self-bodying postulate. The results in this investigation revealed a direct linear relation of increase in yield stress and apparent plastic viscosity with rise in alcohol concentration. This could be seen in the fact that all the plastic viscosities and yield values are generally higher in formulation A (i.e. surfactant 1 part, alcohol 11 parts) than in formulation E (surfactant 1 part alcohol 7 parts) in Table IV - 1 . This is also in agreement with self-bodying phenomena. The thixotropy-alcohol relationship is not however, linear with increase of alcohol concentration but seemed to depend on the alcohol/surfactant ratio with the optimum consistency as the ratio of around 9:1 or 10:1.

Conclusively therefore, it can safely be said that for CTAB and cetostearyl alcohol as mixed emulsifiers, a ratio of 1:9 or 1:10 was found to be optimum for producing rheological stable emulsion with any appropriate consistencies but at ratio of 1:10 will give a higher corresponding yield values.

The B.P and B.P.C. recommend a ratio of alcohol/surfactant of 9:1 for some alcohol/ionic surfactants mixed emulsifiers in Aqueous Cream and Emulsifying Wax and a ratio of 10:1 for cetrimide B.P.C. A ratio of about 4:1 has generally been recommanded for alcohol/nonionic surfactants like the chlorhexidine which have about 21% $^{w}/_{w}$ oil phase.

CONCLUSION

In the preceeding chapters, the 'self-bodying action' of mixed emulsifiers of the CTAB as surfactant and cetostearyl alcohol has been studied. The effect of temperature fluctuations and concentration of such mixed emulsifiers were also examined. The ratio of surfactant/alcohol in such a mixed emulsifier has also been studied with respect to their rheological properties as are affected by the fluctuating tropical temperatures. A commercial sample of clotrimazole 1% w/w cream has also been examined for comparism.

In the systems investigated, it has been observed that emulsions formed with cationic surfactant/long chain alcohol come to an equilibrium rheological state within few hours after preparation. From the range of macroscopical and rheological results, the data obtained showed that comparative studies on all emulsions must be standardized rigidly with respect to time, shear history, temperature during emulsification, the rate of cooling and the emulsification process, whether by simple mixing and cooling or with the aid of homogenizer and the efficiency of such homogenizer.

It has also been observed that the temperature of maximum stability of emulsion systems cannot be accurately determined at lower temperatures of 10^{o} or less for various reasons.

1. It is concluded from the results of experiments obtained in this laboratory that the data support the theory which relates semi-solid nature of oil-in-water emulsions stabilised by mixed emulsifier of the cationic surfactants/ long chain alcohols to gel networks formed in the continuous phase.

2. The elegance and feel of all emulsions studied increase as the mixed emulsifiers increase within the range of concentrations studied. The rheological parameters investigated upon, that is the apparent plastic viscosity, the yield value and the thixotropic break-down all increase progressively with increased mixed emulsifier concentration. The increase in consistencies occur progressively as more alcohol diffuses into the continuous phase to interact with the surfactant solution and build up more network structures.

3. The consistency of most emulsions increase to a maxium with increase temperature from 10^{o} to 20^{o} - 37^{o} and progressively decrease therefrom. The initial increase could be attributed to increase in Brownian motion of the particles while the decrease with rise in temperature could be attributed to the gel network in the continuous phase responsible for the consistency getting weakened and becoming true smectic phase and at higher temperatures the smectic phases in some cases changing to isotropic phase. The temperature of maxium consistency, Tmax, has been shown in this work to depend on the type of formulation (surfactant/alcohol ratio) and to some degree on the mixed emulsifier concentration. A commercial sample of Clotrimazole cream (Canesten Bayer) has Tmax. around 20^{o} but decrease steeply with increase in temperature therefrom suggesting that it may not be ideal to tropical climate as far as a physical stability is concerned depending on the length of time and the height of temperature the product is exposed to.

4. The efficiency of mixed emulsifier of surfactant/long chain alcohol type depends to a greater extent on the surfactant/alcohol ratio. Ratios of 1:9 and 1:10 have been found to be optimum for a formulation with CTAB and cetostearyl alcohol. All the various rheological parameters can be selectively modified individually by careful alteration of either the surfactant/alcohol ratio or the concentration of the mixed emulsifier and sometimes the storage temperature of the finished product since they change to different extent with these changes.

Further work in this field could be extended by a comprehensive diffusional studies on creams of these consistencies within the fluctuating tropical temperatures. This, I am sure, will give a greater insite in the depth of knowledge on drug availability from such formulations which are commonly used in this part of the world.

REFERENCES

1. Abdullah, Mustapha (1982) Dept. of Pharm. Chem. A.B.U., Zaria, Personal Communication.

2. Abubakar, M. (1981) Unpublished data.

3. Arrhenius, S. Z. (1886) Physik Chem. 1, 631.

4. Axon, A. (1956), J. Pharm. Pharmacol. 8, 762.

5. Barry, B. W. (1971) J. Soc. Cosmetic Chem. 20, 487

6. Barry, B. W. (1969) J. Pharm. Pharmacol, 21, 536.

7. Barry, B. W. (1975) Advances in Colloid and Interface Science 5, 37.

8. Barry, B. W. and Shotton, E. (1967)
   (a) J.Pharm. Pharmacol. 19, 110S
   (b) J.Pharm. Pharmacol. 19, 121S

9. Barry, B. W. and Shotton, E. (1969) J. Pharm. Pharmacol. 21, 242

10. Barry, B.W. and Saunders, G. M. (1968)
    (a) J. Colloid Interface (1968)
    (b) ibid 34, 300.

11. Barry, B. W. and Saunders, G. M. (1970 b) J. Pharm. Pharmacol 22S, 130
    (1970 a) J. Pharm. Pharmacol, 21, 607.

12. Barry, B. W. and Saunders, G. M. (1971 a) J. Colloid. Interface, 35, (1971 b).

13. Barry, B. W. and Saunders, G. M. (1971 b) ibid, 36, 130.

14. Barry, B. W. and Eccleston, G. M. (1973) Journal of Texture Studies, 4, 53.

15. Barry, B. W. and Grace, A. J. (1972) J. Pharm. Sci. 61, 335

16. Barry, B. W. and Mayer, M. C. (1973) ibid 62, 1343.

17. Becher, P. (1965). Emulsion Theory and Practice; 2nd Edition, New York, Reinhold.

18. Ben-Kerrour et al (1970). Intern. J. Pharm. 5, 1

19. Bourvet, E. and Bardet, L. (1981) ibid 8, 241.

20. Boylan, J. C. (1966). J. Pharm. Sci. 55, 710

21. Boylan, J. C. (1967) ibid 56, 1164

22. Boylan, J. C., Dekay, G. H. and Banker, G. S. (1962) ibid 51, 742

23. British Pharmacopoeia (1980)

24. British Pharmaceutical Codex 1973

25. Carless, J. E. (1967) in Bentley Textbook of Pharmaceutics. Edited by E. A. Rawling 8th Edition. Beilliere Tinda, London Chapter 9

26. Cheng, D. C. H. (1965) Rheo Acta 4, 257.

27. Chun, A. H. C., Joslin, R. S. and Martin, A. N. (1954) Drug and Cosmetic Ind. 82, 164

28. Cooper, F. A. (1937) J. Soc. Chem. Ind. 56,

29. Cockbain, E. G. (1946) Trans Faraday Soc. 36, 651.

30. Davis, R.E.M. and Rawson, J. M. (1957) J. Pharm., London, 9, 672.

31. Davis, S. S. (1969) (a) J. Pharm. Sci. 58, 411
(b) ibid 58, 412

32. Davis, S. S.; Shotton, E. and Warbarton, B. J. Pharm. Pharmacol (1969) 21, supp. 1575.

33. Europian Pharmacopoeia (1971) Volume II

34. Eirich, F. (1956). Rheology Theology and Applications. Academic Press, New York, Volume I p. 431 and Volume III (1960) p 145.

35. Ekman, B. O. and Sjoholn Inguor (1978) J. Pharm. Sc. 67, 5.

36. Ekwal, Z.; Mandel, L; and Fontel, K (1968) Pro. Int. Liq. Cryst. Cont. 2nd. 325

37. Enever, R. P. (1977) In Bentley's Textbook of Pharmaceutics edited by E. A. Rawlings 8th Edition, Chapter 10. Bailliere Tindel, London, 1977.

38. Finkle P.; Draper, H. D. and Hilderbrand, J. H. (1923) J. Am. Soc. 45, 2780.

39. Fischer, E. K. (1950) Colloid Dispersion Willey New York.

40. Ferrenti-Sherley Viscometer-Operation and Servicing Manual. McKennel, 1960.

41. Ferry, J. D. (1961), Viscoelastic Properties of Polymers: London, Willey.

42. Fuertenau, D. W. (1956). J. Phys. Chem. 60, 981.

43. Garret, E. R. (1965) J. Pharm. Sci. 54, 1557

44. Gbefwi, J. Y. (1978). Ph.D. Thesis, University of Bradford.

45. Gore, D. N. and Ashwan, J. (1967) J. Mond. Pharm. 10, 365

46. Griffin, W. C. (1974) in Cosmetic Science and Technology Volume III, Chapter 44. Edited by M.S. Balson and Edward Sagarin. Willey Interscience Publishers.

47. Griffin, W. C. (1949) J. Soc. Cosmet. Chem. 1, 311

48. Griffin, W. C. (1954). J. Soc. Cosmet. Chem. 5, 249

49. Green, H. (1949) Industrial Rheology and Rheological Structure, page 47, John Willey and Sons In. New York.

50. Green H. and Welt Mann, R. (1949) Industrial Rheology and Rheolcgical Structures Chapman and Hall, London.

51. Guisely, K. B. (1970). The relationship between Methoxyl Content and gelling temperature gorose Carbolyl Res. 13, 241

52. Guisely, K. B. (1971). Viscometric determination of a gorose gellin temp. proc. VIIth Int. Seaweed symp. (1971) 455

53 (a) Hamil, R. D. and Petersen, R. V. (1966) J. Pharm. Sc. 55, 1268.

(b) Hans Schott in chapter 24 of Remington's Pharmaceutical Sciences 15th Ed. (1975) Mack Publishing Company, Easton, Pennsylavania.

54. Harper, R. (1953) In Food Stuffs, the plasticity, fluidity and consistency, G. W. Scotton Blair, E. D. Interscience Publishers, Incar. New York; page 201.

55. Higuchi, T. (1960). J. Soc. Cosm. 11, 85.

56. Houwink, R. (1953) Elasticity, plasticity and structure of matter. 2nd ed. Haven Press, Washington D.C.

57. Jetteries, H. D. (1965) Rheo. Acta. 4, 241.

58. Jellinels, J. Stephen (1970) In formulation and function of cosmetics. Willey Interscience Publishers, page 48.

59. Johnsson Bengt and Wenner Stron Hakan (1981) J. Colloid. Interface, 80, 482.

60. King, A. and Mukherjee, L. A. (1939) J. Soc. Chem. Ind. 58, 2431

61. Kitcherner, J. A.; Musselwhile, P. R. (1968) In Emulsion Science. Academic New York, Chapter 2.

62. Kostenbander, H. B. and Martin, N. (1954) J. AphA Sci. Ed. 43, 401.

63. Laurence, A. S. C. and Milled O. S. (1954) Discussion Farady, Soc. 18, 98.

64. Lenk, R. S. (1962) In Polymer Rheology Applied Science Publishers London.

65. Lenk, R. S. (1967) J. App. Poly. Sci. 11, 1033.

66. Lenk, R. S. (1968). Plastics Rheology, pp 194 Macteren, London.

67. Lenk, R. S. (1978) In Polymer Rheology
Applied Sc. Publishers, Lon. Chapter 1.

68. Levy, G. (1962) J. Pharm. Sci. 51, 947.

69. Litner, C. J. (1973) Quality Control in the
Pharm. Industry, Vol. 2. Academic
Press, New York, p. 141.

70. Mattriot, R. H. (1961) J. Soc. Cosmetic Chem.
12, 49.

71. Martin, A. N. Banker, G. S. and Chou, A. H. (1964)
In Advances in Pharmaceutical Sciences
Edited by H.S. Bean et al, Academic Press,
London, 1964, Chapter 1.

72. Martin, A. N.; Swarbrick, J. and Commaratua (1964)
In Physical Pharmacy 2nd edition,
Lea and Fibriger, Philadelphia, 503.

73. Martindale, Extrapharmacopoeia, 27th edition,(1977)
p. 504.

74. McKennel. Ferrenti Ltd., Monton Manchester, 10.
in The Measurement and Control of
Viscosity and Related Flow Properties
Ferrenti (1960).

75. Metrological Observation, Samaru (1980)
(Sheet One) Institute for Agricultural
Research, Ahmadu Bello University,
Samaru, Zaria.

76. Miller, A. A. (1963) J. Poly. Sci. A1, 6, 1857.

77. Mitshi, T; Tahara, S; and Machida, Y. (1966)
Proc. Sci. Toilet Good Assoc. 46, 73

78. Mysels, K. J. (1959) Indroduction to Colloid
Chem. Willey Interscience, N. York.

79. McVean, D. E. and Mattock, A. M. (1961)
J. Pharm. Sc. 50, 785.

80. Ober, S. S.; Vincent, H. C.; Simon, D. E. and
Fedrich, K. J. (1958). J. Am. Pharm.
Assoc. Sci. Ed. 47, 667.

81. Osborn, G. E. and Lee, C. O. (1951)
Bull. nat. Formul. Comm. 19, 13

82. Ostward, W. (1910 a) Kolloid z 6, 103

83. Ostwald, W. (1910 b) ibid 7, 64.

84. Patton, T. F. and Robinson, J. P. (1975)
J. Pharm. Sc. 64, 8 1315.

85. Pickett, J. M. (1978) In Bentley's Textbook of
Pharmaceutics, 8th Ed. Edited by
E. A. Rawlings, chapter 18
Bailliers, Tindal, London, p. 263.

86. Prince, L. M. (1967) J. Colloid Interface, 23
165.

87. Reddy, S. R. and Foglar, H. S. (1981) ibid 79, 101

88. Reiner Makar (1960) Deformation, stain and flow.
An Introduction to Rheology.
Interscience Publishers, New York,
2nd Edition.

89. Renfeld, S. J. (1967). J. Colloid. and Interface
Sci. 24, 358.

90. Rowe, F. I. (1965). J. Pharm. Sci. 54, 7 260.

91. Schwartz, A. M. and Perry, J. W. (1949) in
Surface Active Agents, their chemistry
and technology. Interscience Pub.
New York.

92. Scott-Blair, G. C. (1945) Pharm. J. 154, 3

93. Shangrow, R; Grim, W; and Mattock, A. M. (1961)
Trans. Soc. Rheology 5, 247.

94. Sherman, P. (1963 a) J. Physical Chem. 67, 2531.

95. Sherman, P. (1963 b) Rheology of Emulsions
Pergason Press, Oxford.

96. Sherman, P. (1959) Kolloid Zeitchrift 165,
2492.

97. Sherman, P. (1964) J. Pharm. Pharmacol. 16, 1

98. Sherman, P. (1970) Industrial Rheology Academic Press, London and New York.

99. Sheriff, M. and Enever, R. P. (1979) J. Pharm. Sci. 68, 844.

100. Simon, T. H; DeKay, H. G. and Banker, G. S. (1961) ibid 50, 880.

101. Skauren et al (1949) J. Am. Pharm. Ass. Sc. Ed. 38, 688.

102. Sprowls, J. B. and Beal, U. M. (1966). American Pharmacy 6th Edition, Lippinco Philadelphia.

103. Synge Richard (1975) in 'Nigeria - The land and its People'. Macdonald and Co. Publishers Limited, p. 54.

104. Talman, F. A. J; Davis, D. T. and Rowen, E.M.(Miss) (1967) J. Pharm. Pharmacol. 19, 1215.

105. Talman, F. A. J; Davis, D. T. and Rowen, E.M.(Miss) (1968 a) ibid 20, 513.

106. Talman, F. A. J; Davis, D. T. and Rowen, E.M.(Miss) (1968 b) ibid 20, 810.

107. Talman, F. A. J; and Rowen, E. M. (1970 a) ibid 22, 338.

108. Talman, F. A. J; and Rowen, E. M. (1970 b) ibid 22, 417.

109. Talman, F. A. J; and Rowen, E. M. (1970 c) ibid 22, 535.

110. Tingstad, James, E. (1964) J. Pharm. Sc. 53, 8 966.

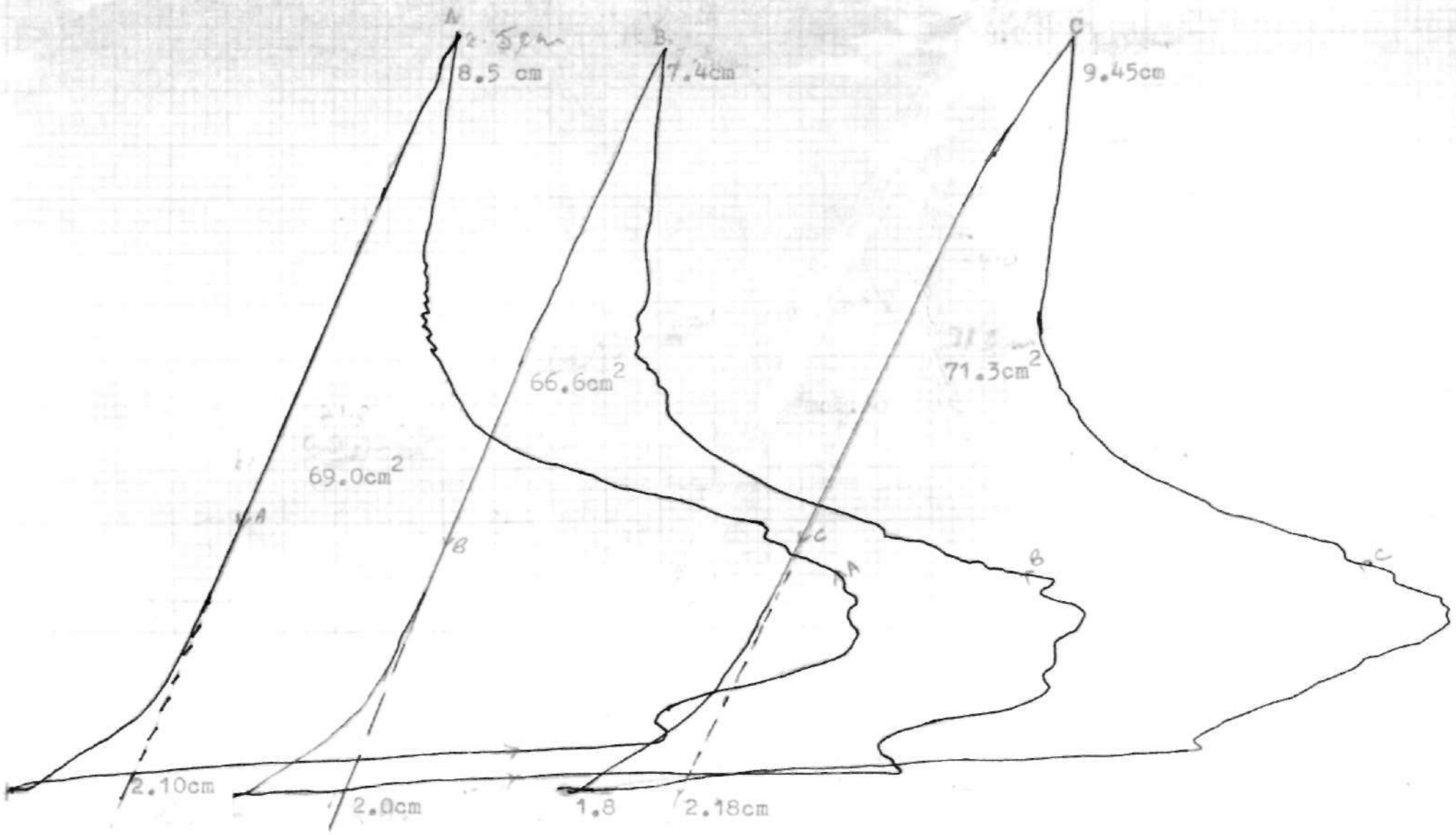
111. Vander Tempel (1953) Rev. Trav. Chem. 72, 419.

112. Van Wazer, J. R; Lynous, J. W; Kin, J. Y. and Colwal, R. E. (1963), Viscosity and Flow Measurement, A laboratory Handbook of Rheology. Interscience Publishers, New York.

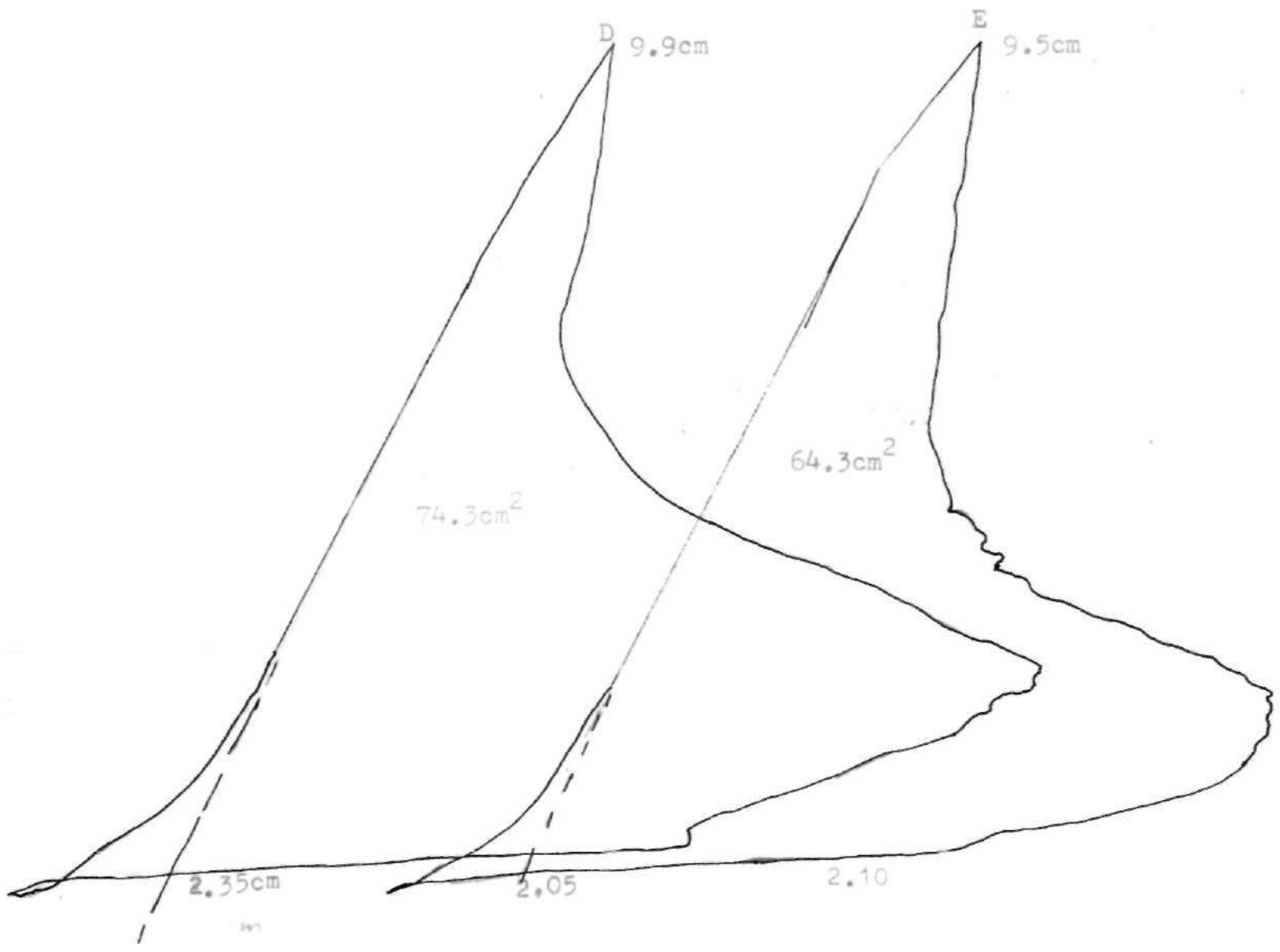
113. William, M. C. (1958) J. App. Phys. 29, 1395.

114. Wood, J. H. and Catacalos, G. (1963) Prediction of rheological aging of Cosmetic Lotion J. Goc. Cos. Chem. 47, 147.

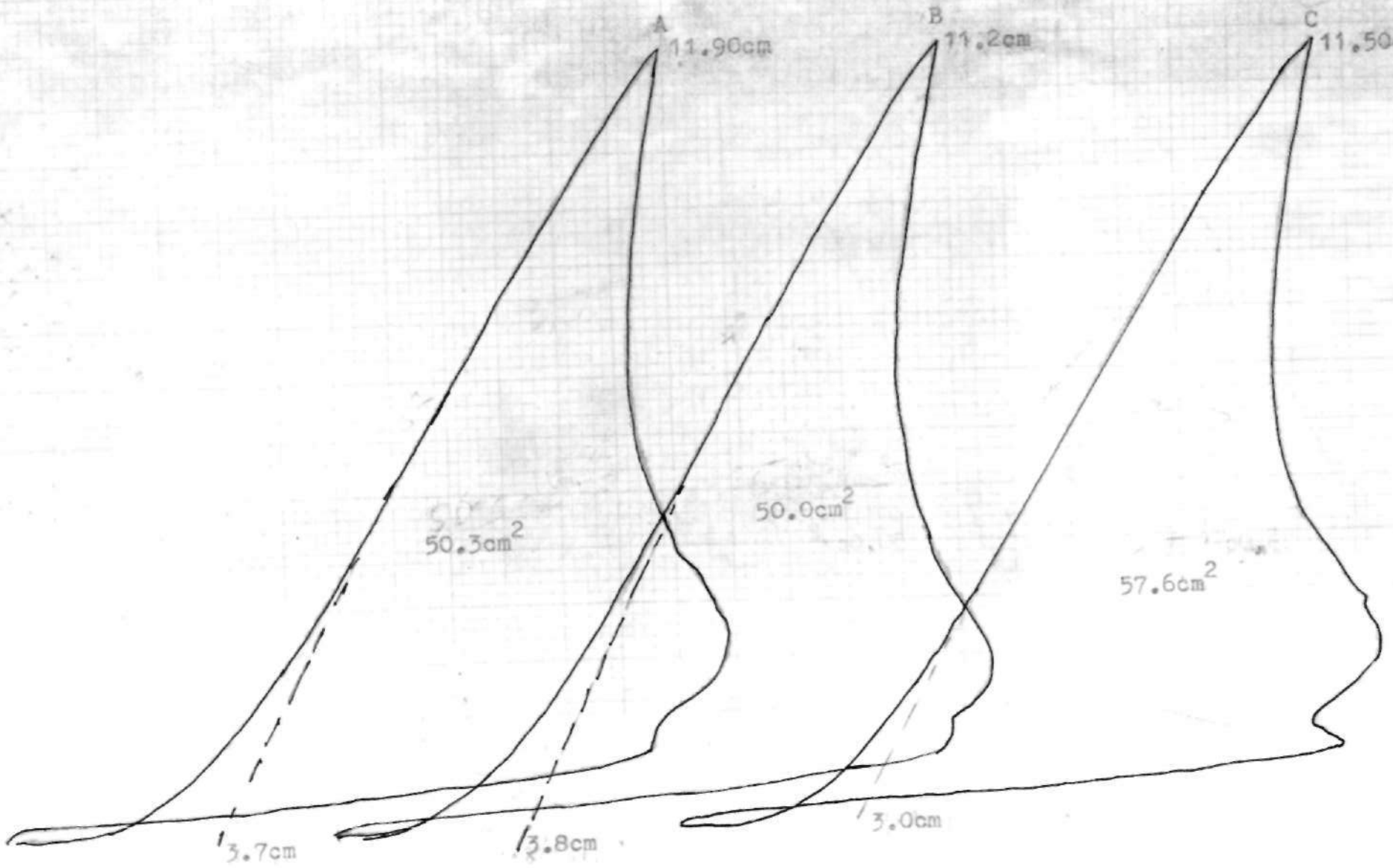
Appendix I Rheograms of a 9% mixed emulsifier emulsion at 10^{o} and shear rate 100 r.p.m.



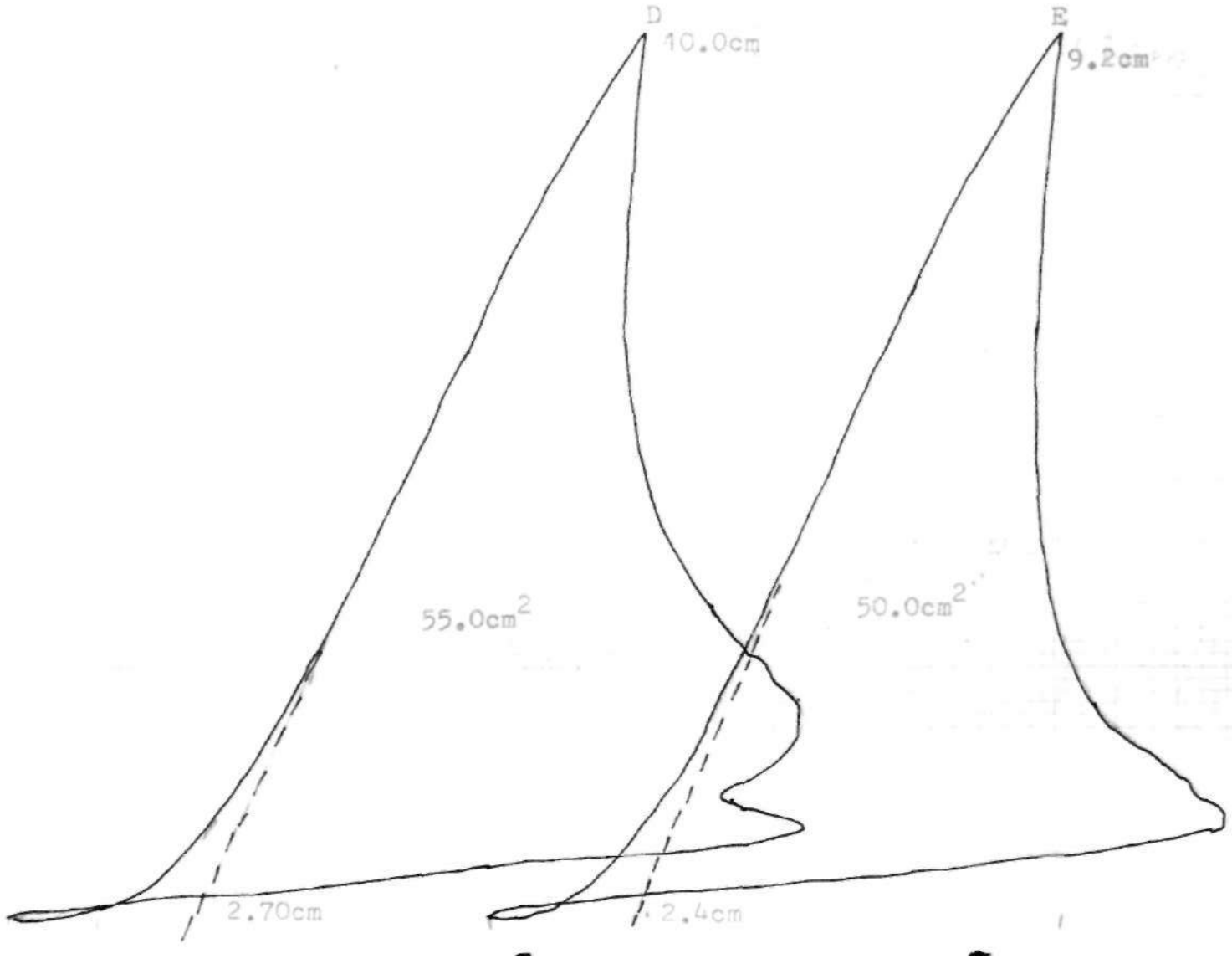
Appendix I Cont'd.



Appendix II Rheograms of 9% mixed emulsifier emulsions at 20° and 100 r.p.m. shear rate

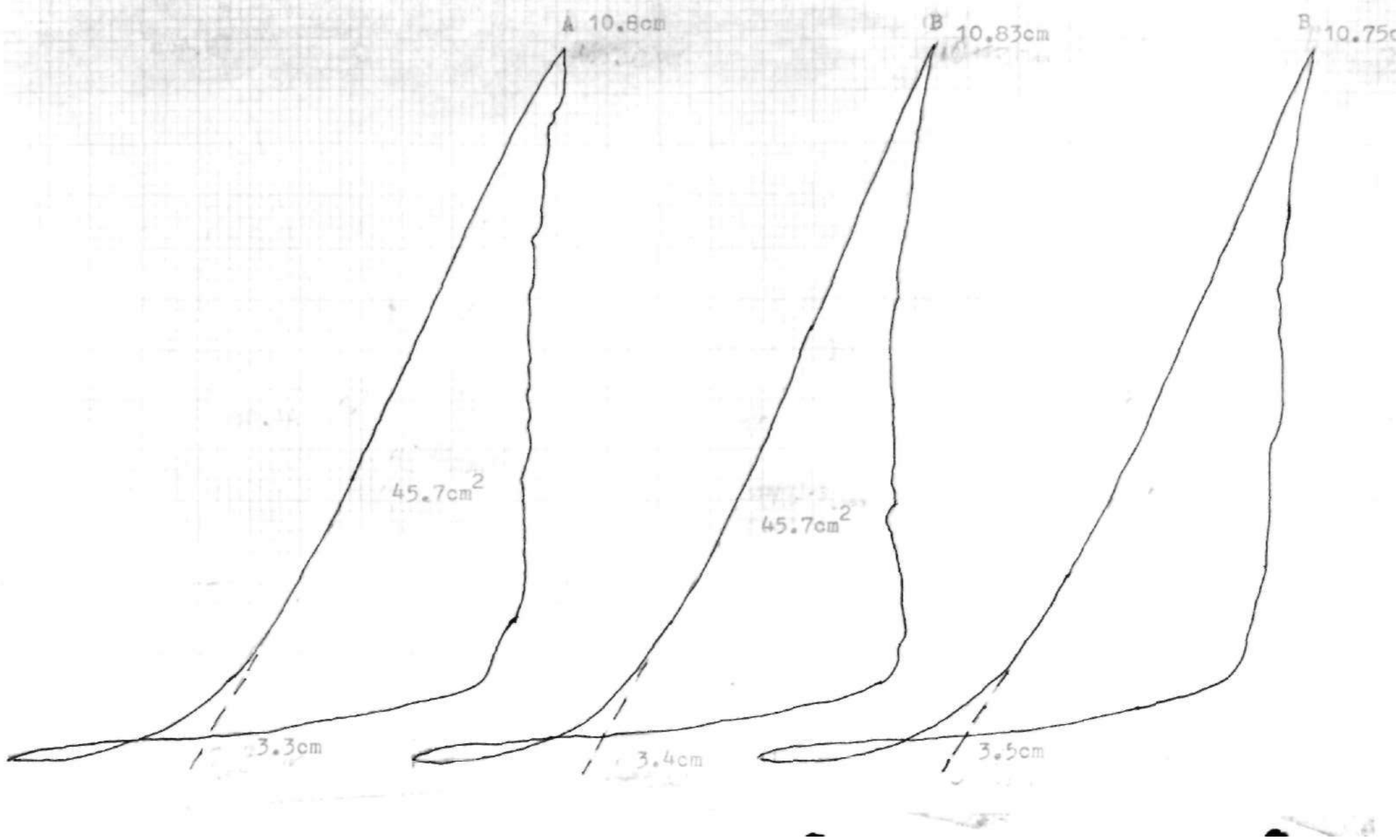


Appendix II cont'd

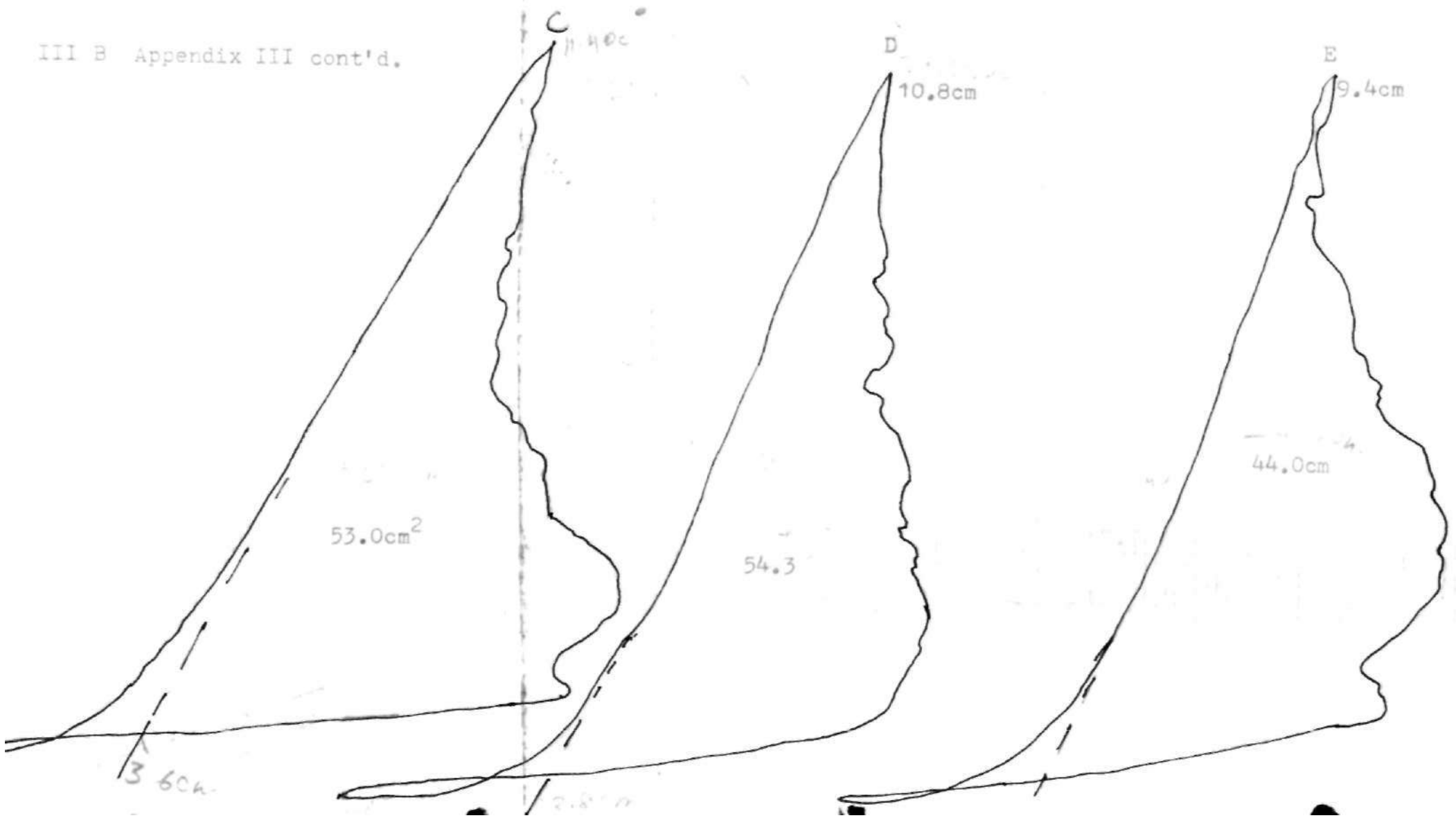


Appendix III

Rheograms of a 9% mixed emusifier emulsion of 27° and 100 r.p.m. shear rate.

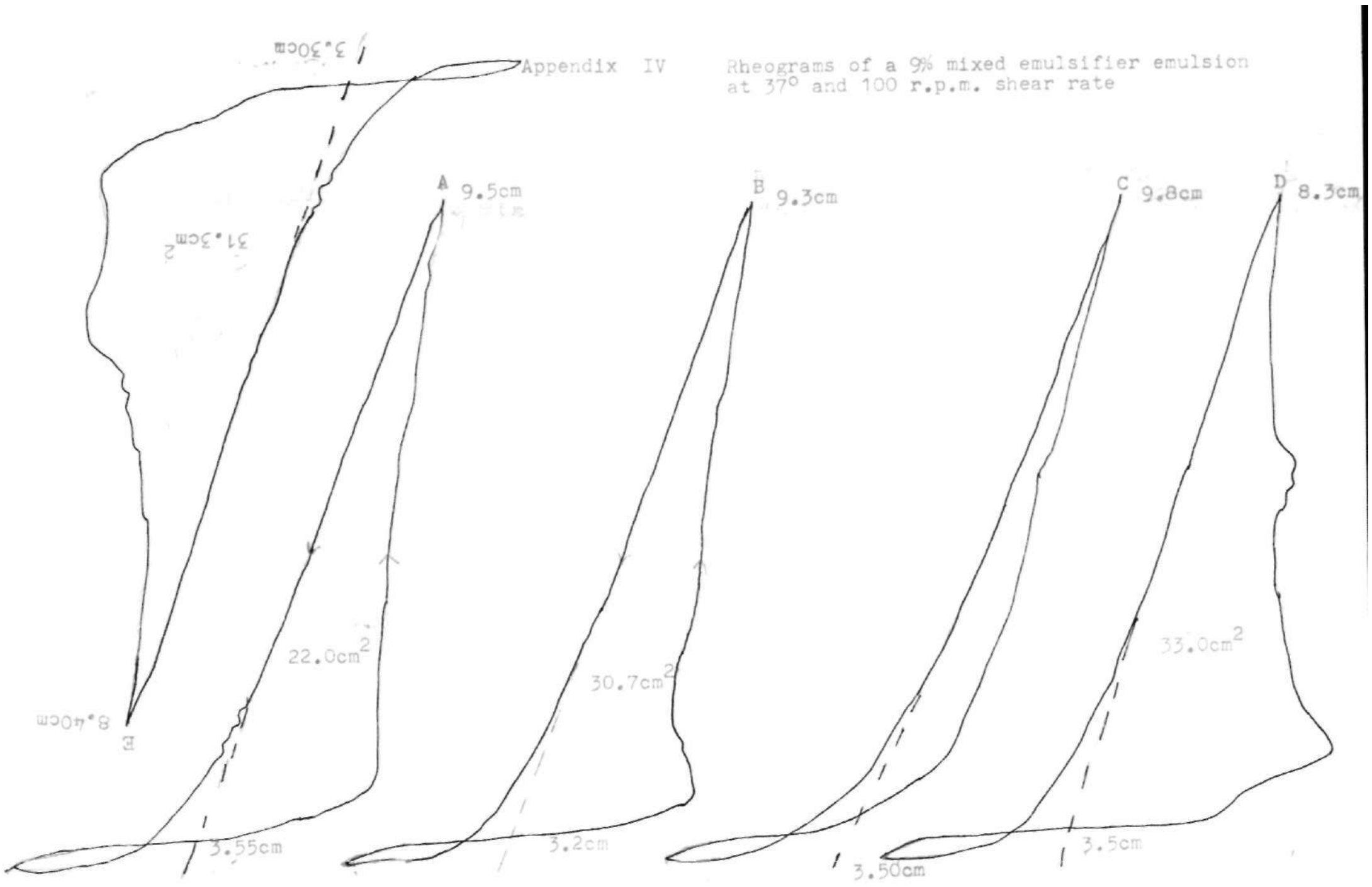


III B Appendix III cont'd.

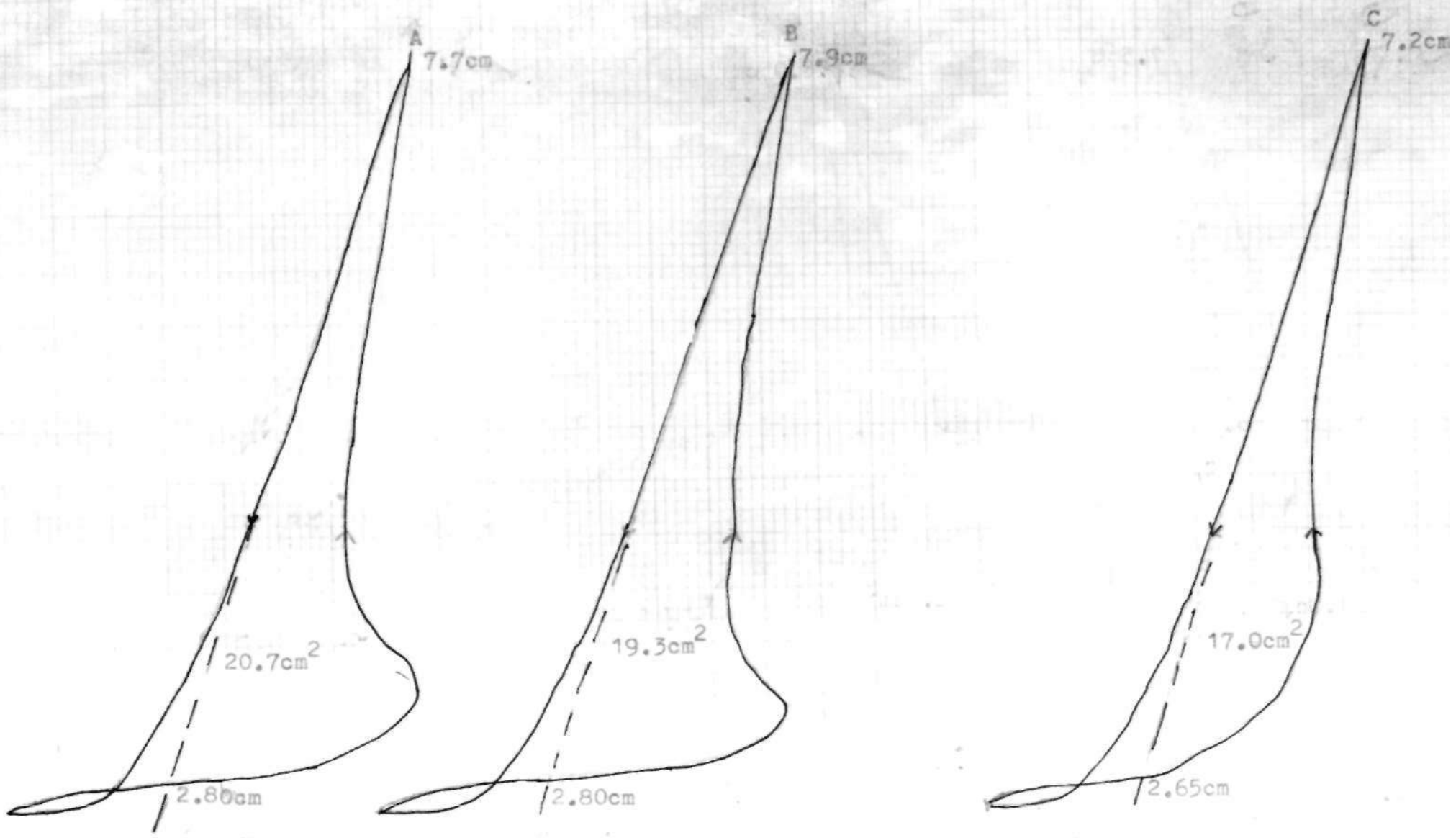


Appendix IV

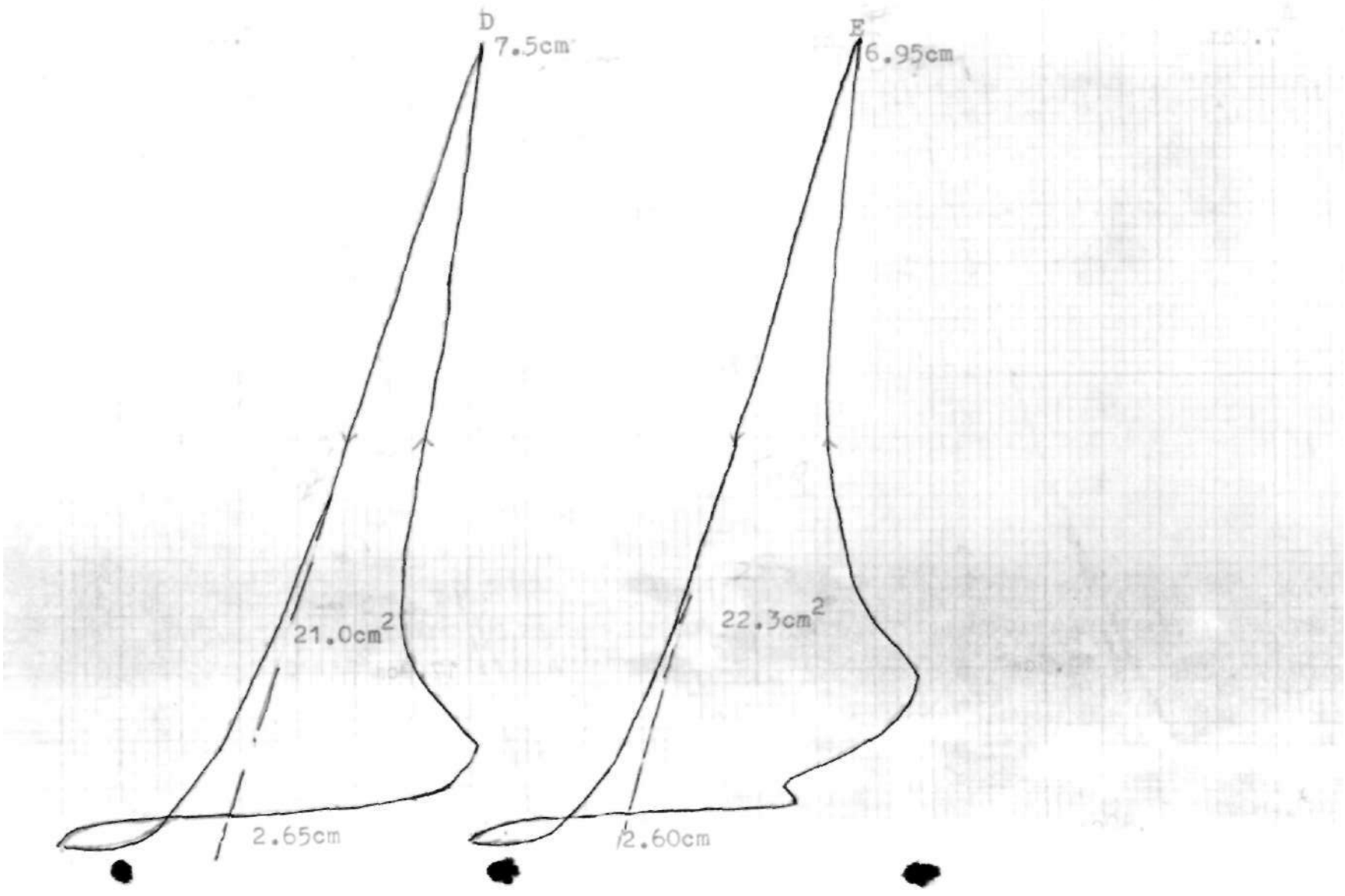
Rheograms of a 9% mixed emulsifier emulsion at 37° and 100 r.p.m. shear rate



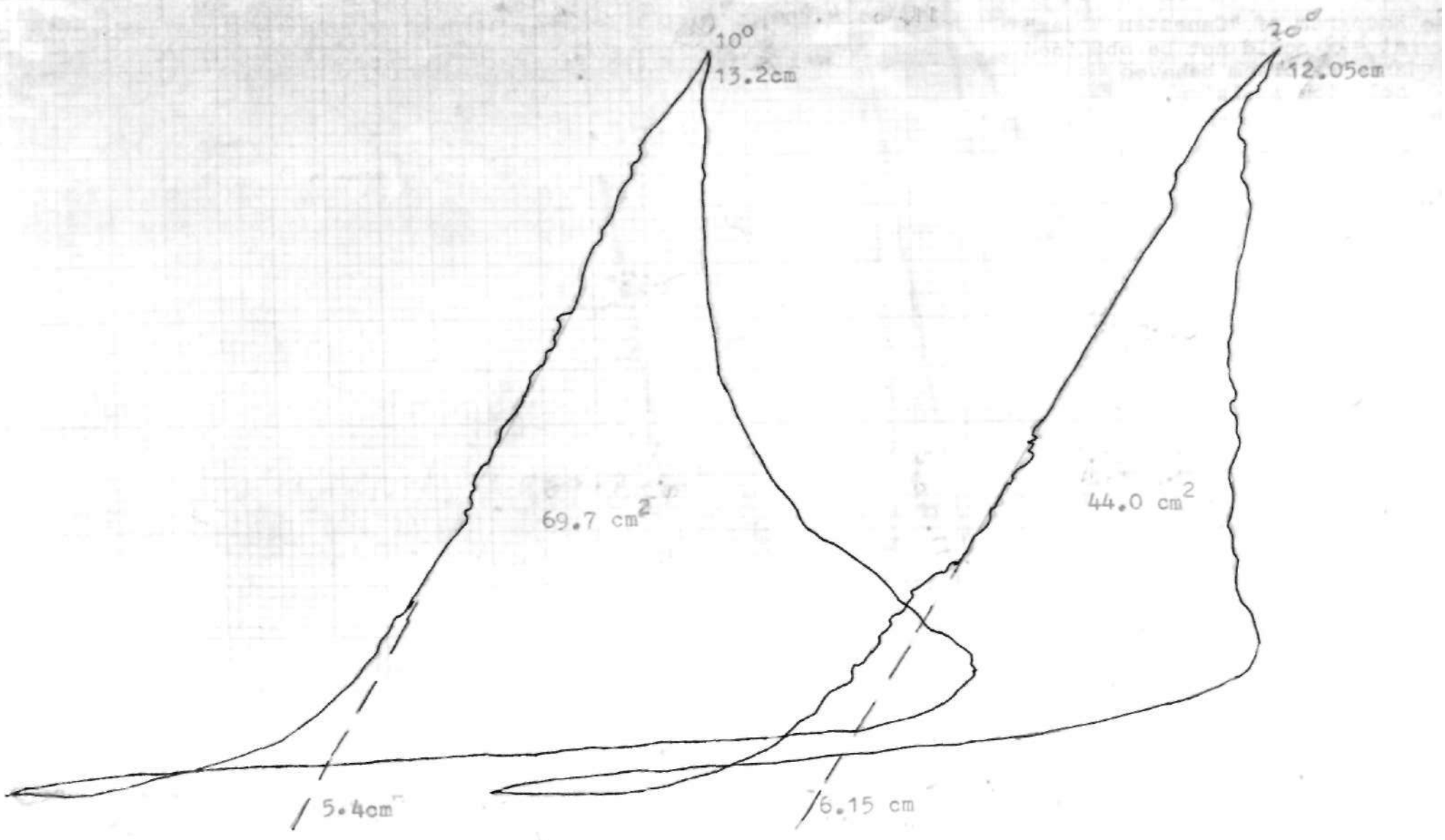
Appendix V Rheograms of a 9% mixed emulsifier emulsion at 45° and 100 r.p.m. shear rate



Appendix V cont'd



VI Rheograms of "Canesten Cream" at various temperatures and 100 r.p.m. shear rate



Appendix VI cont'd.

Note Rheogram of "Canesten Cream" at 45° could not be obtained and the cream behaved as solution emulsion.

